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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN COMPANY** [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HOMA, Fred, L.** [US/US]; 3430 Pine Grove Lane, Kalamazoo, MI 49008 (US). **WATHEN, Michael, W.** [US/US]; 6474 Pepperidge, Portage, MI 49002 (US). **HOPKINS, Todd, A.** [US/US]; 744 Sarah Street, Galesburg, MI 49053 (US). **THOMSEN, Darrel, R.** [US/US]; 6916 Willson Drive, Kalamazoo, MI 49009 (US).

(74) Agent: **YANG, Lucy, X.**; Intellectual Property Legal Services, Pharmacia & Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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(54) Title: A METHOD FOR TREATING HERPES VIRUSES

(57) **Abstract:** The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvrus in a human host in need of such treatment. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpsvrus in a human host in need of such treatment.

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A METHOD FOR TREATING HERPES VIRUSES

FIELD OF THE INVENTION

The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpes viruses in a human host in need of such treatment.

BACKGROUND OF THE INVENTION

The herpesviruses comprise a large family of double stranded DNA viruses. Eight of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans. Several of these viruses are important human pathogens.

HSV-1 is estimated to affect 100 million people in the U.S. Primary infection of HSV-1 usually occurs between the ages of one and four. Cold sores, the visible symptom, typically appear at a later age, with 20-45% of the population over the age of fifteen affected (Whitley, Clin. Intect. Dis., 26:541-555, 1998).

Genital herpes (HSV-2) is the second most common sexually transmitted disease, with approximately 22% of the U.S population infected with this virus (Fleming 1997).

VZV is the causative agent of chicken pox upon primary infection and can recur in adults as zoster.

EBV results in approximately two million cases of infectious mononucleosis in the U.S. each year. It can also cause lymphomas in immunocompromised patients and has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkins disease.

Infection with HCMV often occurs during childhood and is typically asymptomatic except in immunocompriomised patients where it causes significant morbidity and mortality.

HHV-6 is the causitive agent of roseola and may be associated with multiple sclerosis and chronic fatigue syndrome. HHV-7 disease association is unclear, but it may be involved in some cases of roseola. HHV-8 has been associated with Karposi's sarcoma, body cavity based lymphomas, and multiple myeloma.

These viruses are capable of residing in a latent state within the host. Reactivation of latent virus results from response to environmental stimuli (ex. UV exposure, stress,

etc.). Infections or recurrence can be life threatening in immunocompromised patients such as AIDS or transplant patients where HCMV can result in retinitis, pneumonia, and gastrointestinal disease.

The increased immunocompromised population has created an unmet medical need for antivirals against herpesviruses because current therapies do not have a sufficiently broad spectrum against this family of viruses and/or they have limited utility due to toxicity. The present invention provides a method for selectively inhibiting herpesviruses DNA polymerase with compounds that have broad spectrum activity. The method offers a distinct advantage in the treatment of patients in need, particularly immunocompromised patients at risk of infection or reactivation by many members of the herpesvirus family.

SUMMARY OF THE INVENTION

The present invention provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain of the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.

The present invention further provides method for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.

The present invention further provides a compound for the inhibiting of herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said

compound results in a change of the wild type HSV-1 polymerase at amino acid 823 from valine to alanine.

The present invention further provides a compound for inhibiting herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said compound results a change of the wild type HCMV polymerase at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine.

The present invention further provides a mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.

The present invention further provides a mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 – examples of 4-oxo-DHQ and 4-oxo-DHTP compounds.

Figure 2 – Herpesvirus' polymerases amino acid conserved region.

Figure 3 – Recovered virus after serial passage of HSV-1 in presence of 20 μM of compound No. **17**.

Figure 4 – Comparision of Wild HSV-1 and HSV-2 herpesvirus DNA polymerase amino acid sequences alligned by amino acid homology. (Seq. No: 14-19)

Figure 5 – Mutant Herpes Virus DNA and amino acid sequence list. (Seq. No: 1-12)

Figure 6 – Wild HCMV herpesvirus DNA polymerases amino acid sequence. (Seq. No 13)

DETAILED DESCRIPTION OF THE INVENTION

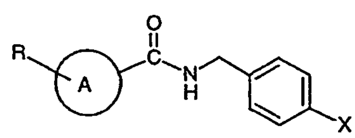
A key enzyme in the replication of all herpesviruses is the virus-coded DNA polymerase. Most of the currently available anti-herpes drugs target the viral DNA polymerase. Drugs such as Foscarnet acts by direct inhibition of the viral polymerase. These drugs are non-nucleoside inhibitors of herpesvirus DNA polymerases. Others such as the nucleoside analogs, Acyclovir, Penciclovir and Ganciclovir must first be phosphorylated to the monophosphate forms by virus encoded kinases and, further phosphorylated to triphosphate by cellular enzymes before they are active inhibitors. The triphosphate forms of these nucleoside analogs inhibit polymerases by competing with the binding of natural

triphosphates and their subsequent insertion into growing DNA strands. These drugs are known as nucleoside inhibitors of herpesvirus DNA polymerases.

One of the limitations of the currently available drugs is that they are active against only a few of the eight human herpesviruses. For example, Acyclovir and Penciclovir inhibit HSV and VZV replication but have poor activity against CMV.

In order to identify antiviral compounds that would have the potential to inhibit replication of most of the human herpesviruses, compounds are *in vitro* screened for inhibitors of herpesvirus DNA polymerase activity. Because portions of the amino acid sequence of the polymerases are highly conserved within the herpesvirus family it is possible to discover small molecules that inhibit herpesvirus polymerases but not cellular DNA polymerases. Using this biochemical approach, several new classes of compounds such as the 4-hydroxyquinoline derivatives (4-HQ), 4-oxo-dihydroquinoline derivatives (4-oxo-DHQ) and 4-oxo-dihydrothienopyridine derivatives (4-oxo-DHTP) were discovered as potent, non-nucleoside herpesvirus DNA polymerase inhibitors. *In vitro* polymerase assays and/or *in vivo* cell culture assays have demonstrated that these compounds inhibit HSV-1, HSV-2, HCMV, VZV, EBV, and HHV-8 replication.

4-Oxo-DHQ and 4-oxo-DHTP are derivatives of formula I



I

wherein ring A is a saturated or unsaturated fused double or triple heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from group consisting of oxygen, sulfur, or nitrogen; and wherein R and X are the appropriated substitutents, respectively.

Examples of 4-HQ compounds, 4-oxo-DHQ compounds and 4-oxo-DHTP compounds are illustrated in **Figure 1.**

Antiviral activity of these examples are shown in Table 1 below. As shown in Table 1, these compounds inhibit HSV-1 and HSV-2 as well or better than the current commercially available drug Acyclovir.

Table 1

Antiviral Activity of 4-oxo DHQ/4-oxo DTHP Against HSV-1 and HSV-2

	Compound IC_{50} (uM)					
virus	**1**	**2**	**3**	**4**	**5**	**ACV**
HSV-1 KOS	2.0	3.8	3.2	3.2	3.3	3.6
HSV-1 F	2.5	2.3	2.2	2.1	2.6	1.3
HSV-1 DJL	2.5	2.6	1.8	2.2	2.7	1.8
HSV-1 Patton	ND	5.3	7.7	4.3	10	9.3
HSV-2 MS	2.0	2.5	2.8	2.5	2.5	10
HSV-2 35D	ND	5.4	5.0	3.2	8.1	6.0
HSV-2 186	2.0	2.3	3.2	2.3	4.2	>10

It has also been discovered that point mutations within the HSV-1 polymerase gene that confer resistance to Acyclovir and other nucleoside analogs do not result in resistance to the 4-HQ, 4-oxo-DHQs or 4-oxo-DHTPs. Serial passage of wild type HSV-1 in the presence of 4-oxo-DHQ results in the isolation of mutants that are highly resistant (>20 fold increase in the IC_{50}) to these compounds while retaining sensitivity to nucleoside inhibitors such as Acyclovir.

In order to determine the mechanism of action of 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds against herpes viruses, mutants resistant to these compounds are isolated by serial passage of the virus in the presence of a 4-oxo-DHQ compound. Sequencing analysis of HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ identifies that HSV-1 (KOS strain) polymerase protein and its homologous HSV-2 have a conserved region (a binding domain), which is a critical contact point for these compounds. While amino acid numbering of the DNA polymerase may vary between strains of HSV-1 and HSV-2, this binding domain encompassing the HSV-1 (KOS) strain amino acid 823 is highly conserved in herpesviruses and can be identified by alligning the homologous amino acids of this domain as shown in Fig 2.

In HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ and similar compounds, a change of valine to an alanine at the binding domain provides full resistance.

In the HSV-1 DNA polymerase, resistance is also found when a valine changes to methionine at amino acid 823 but only when accompanied by a second amino acid change.

Isolation of HCMV resistant to 4-oxo-DHQ's is found to be very difficult. Comparison of the amino acid sequence of the HSV polymerase (Y-G-F-T-G-<u>V</u>-Q-H-G) and HCMV polymerase (Y-G-F-T-G-<u>V</u>-V-N-G) in the region of amino acid 823 (underlined amino acid) shows that there is a second valine at position 824 in the HCMV

polymerase. In vitro assay using mutant HCMV polymerases demonstrates that full resistance to the 4-oxo-DHQs requires changes at both amino acids 823 (a valine to alanine) and 824 (a valine to leucine). A HCMV polymerase gene containing V823A and V824L mutations is used in marker rescue experiments to generate a viral mutant. This mutant has an IC_{50} approximately 7-fold above that of wild-type HCMV.

The HSV-1, HSV-2 and HCMV mutants are also found to be resistant to other non-nucleoside inhibitors such as the 4-oxo-DHTP and similar compounds. However, when the binding domain mutants (e. g. HSV-1 V823A, HSV-2-MS V826A, HSV-2-186 V828A, and HCMV V823A/V824L mutants) are tested in plaque reduction assays against a series of nucleoside polymerase inhibitors and the non-nucleoside inhibitor such as Foscarnet, replication of the mutants is found to be inhibited by all of the currently marketed anti-herpes polymerase inhibitors tested.

These studies demonstrate that certain non-nucleosides like 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds bind to a different site on the herpes polymerase than the nucleoside inhibitors and Foscarnet. The valine at the binding domain is conserved in the DNA polymerases of six of the eight human herpesviruses and several animal herpesviruses, and appears to play a critical role in the antiviral activity of the 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds. (See **Figure 2**)

Since mutation at the binding domain negates these non-nucleoside inhibitors' activities, compounds could be tested against wild type polymerases and the mutant polymerases to establish the probability of similar binding. We refer to this property of compounds as interaction with the binding domain. Since compounds that interact with the binding domain have exhibited broad-spectrum activity against herpesviruses, this invention provides a method for selecting compounds to treat individuals such as immunocompromised patients who are afflicted with multple herpesvirus infections.

Definitions

The term " wild-type" refers to a gene or gene product which has the characteristics of that gene or gene product when isolated from a naturally occurring source. A wild-type gene is that which is most frequently observed in a population and is thus arbitrarily designated the "normal" or " wild-type" form of the gene.

In contrast, the term "mutant" refers to a gene or gene product which displays modifications in sequence and or functional properties (i.e., altered characteristics) when

compared to the wild-type gene or gene product. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

IC_{50} refers to concentration of a drug that inhibits virus growth by 50%.

Wild type HSV-1 and HSV-2 strains are listed in **Figure 4**.

Wild type HCMV is listed in SEQ. ID. NO.13.

The term "Iudr" refers to antiviral drug Iododeoxyuridine.

The term "Bvdu" refers to antiviral drug Bromovinyldeoxyuridine.

The term "ACV" refers to antiviral drug Acyclovir.

The term "AraC" refers to antiviral drug Arabinosylcytidine.

The term "AraT" refers to antiviral drug Arabinosylthymine.

The term "AraA" refers to antiviral drug Arabinosyladenine.

The term "GCV" refers to antiviral drug Ganciclovir.

The term "CDV" refers to antiviral drug Cidofovir.

The term "PFA" refers to antiviral drug Foscarnet.

The term "binding domain" refers to a conserved region in herpesvirus DNA polymerases. The herpesvirus DNA polymerases have seven (7) conserved regions. The binding domain is within the thrid conserved region (see Figure 2). When the binding domain contacts with an inhibitor, at least one amino acid in the binding domain mutates and provides the resistance. In general, the binding domain is at an amino acid sequence position 818-829 of the HSV-1 DNA polymerase or the homologous region in other herpes virus DNA polymerases (see Figure 2).

The term "a binding domain mutant herpes virus" refers to a herpes virus containing a binding domain mutation.

More specifically, the binding domain in HSV-1 strains, KOS, F, DJL and Patton are at amino acid sequence position 823. The binding domain in HSV-2 MS-M1 strain is at amino acid sequence position 826. The binding domain in HSV-2 186 strain is at amino acid sequence position 828. The binding domain in HCMV AD 169 strains is at amino acid sequence position 823-824.

The term "XxxxY" refers to an amino acid sequence position xxx, a single amino acid X in wild type is changed to an amino acid Y.

For example, the term "V823A" refers to an amino acid sequence position 823, a Valine found in wild type is changed to alanine in mutant strain.

The term "V824L" refers to an amino acid sequence position 824, a Valine found in wild type is changed to Leucine in mutant strain.

The term "V826A" refers to an amino acid sequence position 826, a Valine found in wild type is change to alanine in mutant strain.

The term "V828A" refers to an amino acid sequence position 828, a Valine found in wild type is change to alanine in mutant strain.

A table of amino acids and their representative abbreviations, symbols and codons is set forth below in the following Table.

Amino acid	Abbrev.	Symbol	Codon(s)					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

MATERIALS AND METHODS

Cell and Viruses

African green monkey kidney cells (Vero) and human foreskin fibroblast cells (HFF) and herpes viruses can be obtained from the American Type Culture Collection (ATCC). Media is defined as Dulbecco's modified Eagle media (DMEM) containing 10% fetal bovine serum (FBS) and supplemented with antibiotics. Cells are maintained in media at 37°C in a humidified atmosphere of 5% CO^2. HSV-1 strains F, Patton and DJL, HSV-2 strains MS, 35D and 186, and HCMV strain AD169 are used in these studies. Strain DJL is a clinical isolate of HSV-1 isolated in our lab from a primary oral lesion.

Measuring IC_{50} of a Compound of Interest That Inhibits Herpes Viruses

Preparation of Virus Stocks: HSV-1 and HSV-2 stocks are grown in Vero cells. HCMV stocks are grown in HFF cells. Approximately 1 ml of media containing sufficient virus to infect approximately 0.1% to 1% of the cells (multiplicity of infection of 0.001 to 0.01 PFU/cell) is added to a T-150 cell culture flask containing a confluent monolayer of cells. The cells are incubated at 37°C for approximately 1 hour. Approximately 50 ml of media is then added to the flask and the cells are incubated at 37°C until viral cytopathic effect (cpe) is apparent in 100% of the cells. The flask is then placed at –80°C for at least 30 min. The flask containing frozen media and cells is placed in a 37°C water bath until the media is thawed. This process disrupts the cells and releases virus into the media. 1 ml aliquots of media containing virus are dispensed into tubes and stored at –80°C. These aliquots of media containing virus are referred to as virus stocks.

Titrating Virus Stocks: Aliquots of virus are thawed at 37°C and serially diluted (10 fold dilutions) in media. 0.1 ml of each dilution of virus is placed in a single well of 24-well cell culture dish containing a confluent monolayer of cells (Vero cells for HSV-1 and HSV-2, HFF cells for HCMV) and incubated at 37°C for 1 h. The virus innoculum is then removed and 1 ml of media containing 0.8% carboxymethylcellulose (CMC) is added to each well of the dish. The dish is incubated at 37°C for approximately 2-3 days (HSV-1 and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the cell monolayer. Plaques can be observed and counted microscopically or by staining the cells with 0.1% crystal violet in 20% ethanol. The virus titer which is expressed as plaque forming units (PFU) per ml is obtained by counting the plaques in a well and correcting for the dilution of the viral innoculum.

Plaque Reduction Assays: Antiviral activity of compounds against herpesviruses such as HSV-1, HSV-2, or HCMV can be measured using plaque reduction assays. 0.1 ml of media containing approximately 50 PFU of virus is added to each well of a 24-well cell culture dish containing a confluent monolayer of cells (Vero cells for HSV-1 and HSV-2, HFF cells for HCMV). Compounds are dissolved in 100% DMSO and diluted in 100% DMSO as 200x stocks of the desired final drug concentration. Typically 5-6 two-fold dilutions are prepared for each compound. Dilutions of compounds are then added to media containing 0.8% CMC resulting in a final 1x drug concentration. After the virus-infected cells have incubated for 1 h at 37°C, the virus innoculum is removed and 1 ml of media containing 0.8% CMC and the various concentrations of compound is added to each well of the dish.

The dish is incubated at 37°C for approximately 2-3 days (HSV-1 and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the cell monolayer. Plaques can be observed and counted microscopically or by staining the cells with 0.1% crystal violet in 20% ethanol. Virus inhibition is determined for each drug concentration by comparing the number of plaques in drug-containing wells to control wells that did not contain drug. Antiviral activity of a compound is expressed as the concentration of compound predicted to reduce the number of plaques in a well by 50% (IC_{50}). The IC_{50} values are calculated by plotting the per cent inhibition vs. concentration of compound using EXCEL software for linear regression.

Selection of 4-oxo-DHQ resistant HSV-1 and HSV-2

Vero cells are plated out at a density of $3.5x10^5$ cells per well in a six well tissue culture plate. Cells are infected with HSV-1 KOS at a multiplicity of infection (moi) of 0.1 pfu/cell and 1 h post infection the cells are overlayed with 3 ml media containing 20 uM of a 4-oxo-DHQ. Cultures are incubated for 20 h at 37°C, freeze/thawed to release cell-associated virus, and 0.1 ml of culture is used to infect a new monolayer of Vero cells (one passage). Serial passage is repeated seven times in the presence of 20 uM drug. Virus isolates are then plaque purified three times prior to preparation of stocks. Virus recovered from each passage in the presence of compound No. 17 is shown in **Figure** 3. 4-oxo-DHQ resistant HSV-1 and HSV-2 may also be selected by the marker transfer method described below using wild-type HSV DNA and the corresponding mutant HSV polymerase gene.

Marker Transfer of a HCMV Mutation

A plasmid containing the wild-type HCMV polymerase gene is modified to contain the V823A or V823A and V824L mutations using a site-directed mutagenesis Kit (Stratagene Corp.) and following the manufactures's protocol. HFF cells are plated into T25 tissue culture flasks to achieve 80% confluency at the time of the transfection. Wild type HCMV AD169 DNA and plasmid DNA containing the mutant HCMV polymerase gene are mixed at a ratio of 1:2 (2ug of viral DNA to 4 ug of plasmid DNA). DNA's are transfected using superfect transfection reagent according to methods recommended by the manufacturer (Quiagen Inc.). Cells are harvested five days posttransfection, freeze-thawed to release virus and half of the sample is used to infect HFF cell monolayers. Cells are overlayed with media containing 20 uM 4-oxo-DHQ compound **2** (see Figure 1). Serial

passage is repeated seven times in the presence of 20 uM compound **2** and virus isolates are then plaque purified three times prior to preparation of viral stock.

Isolation of HSV and HCMV viral DNA

HSV DNA is purified from the cytoplasm of infected Vero cells. Vero cells (50 % confluent) are infected at an multiplicity of 0.01 PFU/cell. At 3-5 days postinfection infected cells (100% cpe) are harvested by centrifugation at 1000 rpm in a Beckman GS-6R centrifuge. The pelleted cells are resuspended in TE buffer and placed on ice for 15 minutes. NP-40 is then added to a final concentration of 0.2% and incubated on ice for a further 15 minutes. The cells are centrifuged at 2000 rpm for 10 minutes in a Beckman GS-6R centrifuge. The supernatant is removed and EDTA is added to a final concentration of 20 mM followed by the addition of SDS to a final concentration of 0.3% and proteinase K to a concentration of 50 ug/ml then incubated at 45C for 2 hours. HCMV DNA is isolated by infecting HFF cells (25% confluency) with HCMV at an multiplicity of 0.1 PFU/cell. Cells and media are harvested 5-7 days postinfection (100% cpe) and subjected to low speed centrifugation to remove intact cells and cell debris followed by a high speed spin to pellet virus particles (2500 rpm's in a Beckman SW28 rotor for 1 hour). Following incubation of the HSV and HCMV samples, 1.5 volumes of saturated NaI is added to the digested extract and the refractive index is adjusted to 1.434 –1.435. Ethidium bromide is added to a final concentration of 50 ug/ml. The samples are loaded into a VTI 50centrifuge tube and spun for 24 hours at 45,000 rpm. The DNA band is harvested extracted three times with n-butanol, then dialyzed against TE buffer followed by a dialysis against 95% ethanol and a final dialysis against TE buffer.

DNA Sequencing

HSV-1, HSV-2 or HCMV viral DNA's are sequenced directly using an ABI377 fluorescence sequencer (Perkin Elmer Applied Biosystems, Foster City, CA) and the ABI BigDye PRISMTM dRhodamine Terminator Cycle Sequencing Ready Reaction Kit with AmpliTaq FSTM DNA polymerase (PE Applied Biosystems). Each cycle sequencing reaction contained about 1.0 ug of purified viral DNA. Cycle-sequencing is performed using an initial denaturation at 98°C for 1 min, followed by 50 cycles: 98°C for 30 sec, annealing at 50°C for 30 sec, and extension at 60°C for 4 min. Temperature cycles and times are controlled by a Perkin-Elmer 9700 thermocycler. Extension products are

purified using CentriflexTM gel filtration cartridges (Edge BioSystems, Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 750 x g for 1.5 min at room temperature. Column-purified samples are dried under vacuum for about 40 min and then dissolved in 4 ul of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples are then heated to 90°C for two min, and held at 4°C until loading. 1.5 ul of each sample is loaded into a single well of the ABI377 sequencer. Sequence chromatogram data files from the ABI377 are analyzed with the computer program Sequencher (Gene Codes, Ann Arbor, MI), for assembly of sequence fragments and correction of ambiguous base calls. Generally sequence reads of 600-700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers at different locations until all sequencing ambiguities are removed.

The entire coding region of the polymerase genes from both the parent strains and the resistant viruses are sequenced. The DNA sequencing is done using viral DNA as the template thus avoiding cloning of the polymerase genes. The amino acid sequence of the DNA polymerases of HSV-1 KOS, F, Patton and DJL and HSV-2 MS and 186 are compared in **Figure 4**. Amino acids that are identical for the six polymerases are shaded in black while regions where amino acid differences are found are shaded in gray. The amino acid sequence of the four HSV-1 polymerases are essentially identical with only a few minor changes noted between the different HSV-1 strains. The majority of amino acid changes are found when the sequences of the HSV-1 and HSV-2 polymerases are compared.

Isolation and Characterization of HSV-1 and HSV-2 Mutants That Are Resistant To the 4-oxo-DHQ's and 4-oxo-DHTP Compounds

A panel of viruses consisting of four strains of HSV-1 (KOS, F, DJL, Patton) and three strains of HSV-2 (MS, 35D, 186) are tested in a plaque reduction assay against four different 4-oxo-DHQ compounds (# **1**, **2**, **4**, **5** as shown in Figure 1), and one 4-oxo-DHTP compound (# **3** as shown in Figure 1) and against Acyclovir. The six drugs inhibited replication of the seven virus strains with IC_{50} values ranging from 2-10 μM (Table 1). In order to select for 4-oxo-DHQ resistant mutants, HSV-1 strains KOS, F, and DJL along with HSV-2 strains 186 and MS are serially passaged in the presence of 20 uM compound

1. Following the seventh passage, 4-oxo-DHQ resistant virus from each strain are plaque purified three times and high-titer stocks are made. All of the resistant HSV mutants grew to high titers in Vero cells, indicating that the mutations in the resistant isolates did not significantly impair their growth. The mutants selected with 4-oxo-DHQ compound **1** exhibited >10 fold increase in IC_{50} when tested in a plaque reduction assay against 4-oxo-DHQ compound **1** Data are shown in Table 2.

Table 2

4-oxo-DHQ Resistant Virus of HSV-1 and HSV-2

Virus Mutants	Compound 1 IC_{50} (uM)	Amino Acid Change in HSV DNA Polymerase
HSV-1 Kos-M1	>20	- V823A
HSV-1 F-M1	>20	- V823A
HSV-1 DJL-M1	>20	-V823A
HSV-2 MS-M1	>20	- V826A
HSV-2 186-M1	>20	- V828A

*HSV-1 and HSV-2 isolates grown in the presence of 4-oxo-DHQ select for resistant virus.

DNA sequence analysis of the 4-oxo-DHQ resistant mutants (HSV-1 KOS-M1, HSV-1 F-M1, HSV-1 DJL-M1, HSV-2 186-M1, HSV-2 MS-M1) demonstrated that all five mutants contained a single point mutation of T to C at the binding domain resulting in a Valine to Alanine amino acid change.

<u>Isolation and Characterization of A HCMV Mutant That Is Resistant to The 4-oxo-DHQ's and 4-oxo-DHTP Compounds</u>

In order to select for a 4-oxo-DHQ HCMV resistant mutant, virus (strain AD169) is serially passaged in the presence of 20 uM a 4-oxo-DHQ. Although we could readily select for HSV mutants using this procedure we failed to isolate an HCMV mutant, even when the virus is passaged at low drug concentrations (<5 uM). Comparison of the amino acid sequence of the HSV polymerase, Y-G-F-T-G-<u>V</u>-Q-H-G, and HCMV polymerase, Y-G-F-T-G-<u>V</u>-V-N-G, in the region of amino acid 823 (underlined amino acid) showed that there is a second valine at position 824 in the HCMV polymerase. In order to determine if both valines need to be changed in order to confer resistance to the 4-oxo-DHQ's, *in vitro* polymerase assays are done using mutant HCMV polymerases containing either V823A or V823A plus V824L (Table 3).

Table 3

HCMV Mutant Polymerase Exhibits Resistance to 4-oxo-DHQ*

Polymerase	Compound 1 IC_{50} (uM)
HCMV (wild)	4.6
HCMV V823A	17.2
HCMV V823A/V824L	42.9

*Generation of the valine to alanine at amino acid 823 of HCMV results in a 3.5-fold increase in resistance.

*Mutation of the amino acid from valine to alanine and amino acid 824 from valine to leucine results in an 9-fold increase in resistance, relative to wild type.

The V823A alone resulted in a 3.5-fold increase in the IC_{50} while the polymerase with the double amino acid change had nearly 10-fold increase in the IC_{50}. In order to isolate an HCMV resistant mutant marker rescue experiments are done. Plasmids containing the mutant polymerase genes are transfected into HFF cells along with wild type HCMV AD169 DNA. The resulting virus is then serially passaged in the presence of 20 uM compound **1** (see figure 1). A 4-oxo-DHQ resistant virus is isolated from marker rescue studies done with the HCMV polymerase gene containing mutations that result in the V823A, V824L amino acid changes, but not with the gene containing V823A change alone. The mutant selected with compound **1** (HCMV AD169-M1) exhibited ~7-fold increase in IC_{50} when tested in a plaque reduction assay compared to Ganciclovir and cidofovir which has a ≤ 2-fold change in sensitivity (Table 4).

Table 4

Plaque reduction assay of 4-oxo-DHQ resistant HCMV*

Drug	HCMV AD169 IC_{50} (μM)	HCMV AD169 – M1 IC_{50} (μM)
Compound 1	0.7	4.7
Ganciclovir	0.9	1.0
Cidofovir	0.3	0.6

*Recombination of wild-type HCMV with a polymerase gene containing the valine to alanine at amino acid 823 and the valine to leucine at amino acid 824 allowed for selection of resistant virus with about 7-fold less sensitivity to compound 1.

*Sensitivity of resistant HCMV virus to Ganciclovir and Cidofovir verifies that the 4-oxo-DHQ's mechanism for inhibiting the polymerase protein is unique

The entire coding region of the HCMV polymerase genes from both the parent strain and the resistant virus are sequenced. The DNA sequencing is again done using viral DNA as the template thus avoiding cloning of the polymerase genes. Comparison of the DNA sequence of the two polymerase genes demonstrated that the resistant mutant contained two point mutations that resulted in the predicted V823A, V824L amino acid changes. As with the HSV resistant viruses these results demonstrate the critical role of the region encompassing amino acid 823 for inhibition of polymerase activity by these compounds.

Antiviral Activity of Nucleoside and Non-Nucleoside Polymerase Inhibitors Against 4-oxo-DHQ Resistant Mutants

In order to determine if the 4-HQ binding domain mutations alter the sensitivity of the HSV-1, HSV-2 and HCMV mutants to both non-nucleoside (4-oxo-DHQ's) and nucleoside inhibitors (e.g Acyclovir and ganciclovir) several of the mutants are tested in plaque reduction assays against a series of non-nucleoside compounds including Foscarnet (PFA), 4-HQ's 4-oxo-DHQ's and 4-oxo-DHTP's (Table 5). The mutants are also tested against a series of nucleoside inhibitors including acyclovir and ganciclovir (Table 5). The activity of these compounds against the mutants is compared to their activity against the wild type strains that are used to isolate the HSV and HCMV mutants. When tested against a number of 4-HQ's, 4-oxo-DHQ's and 4-oxo-DHTP's and other related classes of compounds all of the drugs are found to inhibit the wild type virus with IC_{50} values ranging from <0.1 uM to 30 uM. When these drugs are tested against the resistant viruses they are found to have IC_{50} values 5 to 10 fold higher then the parent virus. There is little if any difference in the IC_{50} values of the nucleoside compounds and the non-nucleoside PFA between the wild type and mutant HSV-1, HSV-2, and HCMV viruses. These results demonstrate that the amino acid change in the binding domain (V823A in the HSV-1 polymerase, V826A in the HSV2-MS polymerase, V828A in the HSV2-186 polymerase, and the V823A/V824L changes in the HCMV polymerase) resulted in resistance to the 4-oxo-DHQ's and 4-oxo-DHTP's, which provides further evidence that these classes of compounds share an affinity for a region we refer to as the binding domain. In contrast, these amino acid changes did not alter the activity of these viruses to other classes of polymerase inhibitors.

Table 5

Antiviral activity of nucleoside and non-nucleoside polymerase inhibitors against HSV-1, HSV-2, and HCMV Isolates selected for 4-oxo-DHQ resistance*

	Plaque Reduction Assay – IC_{50} (μM)					
Drug	**HSV-2 MS**	**HSV-2 MS-M1**	**HSV-1 KOS**	**HSV-1 KOS-M1**	**HCMV AD169**	**HCMV AD169-M1**
6	28.8	>50	24.6	>50	5.1	>16
7	8.8	27.9	6.5	>50	0.3	3.4
8	2.3	>50	5.1	>50	<0.1	1.1
9	0.9	48.7	1.9	>50	<0.1	3.1
10	29.2	>50	15.8	>50	1.1	>16
11	3.0	>50	3.1	>50	0.7	3.9
12	0.4	12.5	1.3	>50	0.2	1.1
13	5.3	>50	5.5	<25	2.7	>16
14	1.6	>50	28.4	>50	0.9	18.4
2	1.3	>50	3.3	>50	0.4	4.0
4	2.1	28.4	4.2	>50	0.6	2.1
3	0.8	>50	4.0	>50	1.5	6.2
15	5.9	>50	>50	>50	0.7	7.7
Iudr	5.0	6.1	1.1	0.8	ND	ND
Bvdu	5.8	5.9	2.1	0.1	ND	ND
ACV	2.4	2.8	3.9	4.4	ND	ND
AraC	0.2	0.1	0.2	0.2	ND	ND
AraT	6.6	3.6	11.6	3.6	ND	ND
AraA	10.6	18.2	26.1	27.2	ND	ND
GCVir	ND	ND	ND	ND	0.8	0.8
CDV	ND	ND	ND	ND	0.4	0.3
PFA	ND	ND	ND	ND	38	<20

*HSV-2 MS, HSV-1 KOS, HCMV AD169: wild type strains
*HSV-2 MS-M1, HSV-1 KOS-M1, HCMV AD169-M1: mutants selected for 4-oxo-DHQ resistance
*ND – Not Done.

Antiviral compounds identified by the present invention can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable excipient, the composition being useful in combating viral infections. Pharmaceutical compositions containing a compound appropriate for antiviral use are prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975).

Antiviral compounds identified by the present invention and their compositions can be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular

injection), topically, orally, or rectally, depending on whether the preparation is used to treat internal or external viral infections.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

Antiviral compounds identified by the present invention and their compositions can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which

are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids,

fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

For internal infections, the compositions can be administered orally or parenterally at dose levels, calculated as the free base, of about 0.1 to 300 mg/kg, preferably 1.0 to 30 mg/kg of mammal body weight, and can be used in man in a unit dosage form, administered one to four times daily in the amount of 1 to 1000 mg per unit dose.

For parenteral administration or for administration as drops, as for eye infections, the compounds are presented in aqueous solution in a concentration of from about 0.1 to about 10%, more preferably about 0.1 to about 7%. The solution may contain other ingredients, such as emulsifiers, antioxidants or buffers.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgment of the attending practitioner.

The antiviral activity of a compound of the invention can be determined using pharmacological models which are well known to the art, or using Test A described below.

The compounds of formula (I) and pharmaceutically acceptable salts thereof are useful as antiviral agents. Thus, they are useful to combat viral infections in animals, including man. The compounds are generally active against herpes viruses, and are particularly useful against the varicella zoster virus, the Epstein-Barr virus, the herpes simplex virus, the human herpes virus type 8 (HHV-8) and the cytomegalovirus (CMV).

CLAIMS

We claim:

1. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

2. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant herpes virus,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

3. The method of claim 1 or 2 wherein the herpes virus is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.

4. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

5. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-1,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-1,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

6. The method of claim 4 or 5 wherein HSV-1 is HSV-1 KOS, HSV-1 F, HSV-1 DJL or HSV-1 Patton.

7. The method of claim 5 or 6 wherein the mutation of a wild type herpes virus to mutant herpes virus is at amino acid 823 from valine to alanine.

8. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

9. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-2,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-2,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

10. The method of claim 8 or 9 wherein HSV-2 is HSV-2 MS, HSV-2 35D, or HSV-2 186.

11. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,

b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain as the wild type herpes virus,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

12. A method of selecting compounds that inhibit herpes viruses comprising:

a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HCMV,

b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain of the mutant HCMV,

c) comparing IC_{50} of step a with IC_{50} of step b; and

d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.

13. The method of claim 8 or 9 wherein HCMV is AD169.

14. The methods of claims 1, 4, 8, or 11 wherein IC_{50} of step b is at least 5 times greater than the IC_{50} of step a.

15. The methods of claims 2, 5, 9, or 12 wherein IC_{50} of step a is at least 5 times greater than the IC_{50} of step b.

16. A use of compounds for manufacturing of medicinals for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.

17. A use of compounds for manufacturing of medicinals for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain

mutant herpes virus is at lease 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

18. The use of claim 17 wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes viruse.

19. The use of claim 17 wherein herpes viruses is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.

20. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at lease 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

21. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.

22. The herpesviral infection of claim 20 or 21 which is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8 infection.

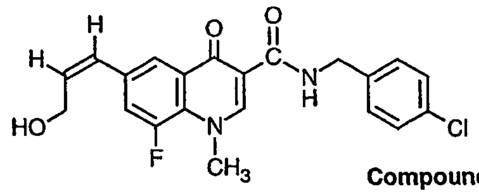
23. A compound for the inhibiting of herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results a change of the wild type HSV-1 polymerases at amino acid 823 from valine to alanine.

24. A compound for inhibiting herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results in a change of the wild type HCMV polymerases at amino acid 823 from valine to alanine and at amino acid 824 from valine to leuline.

25. A mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.

26. A mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

Figure 1 **4-HQ, 4-oxo-DHQ and 4-oxo-DHTP antiviral compounds**



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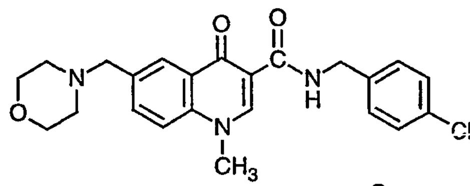

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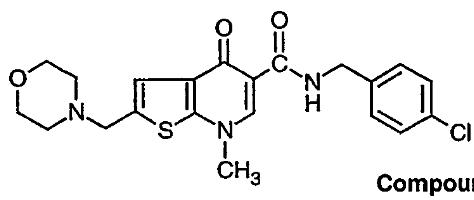

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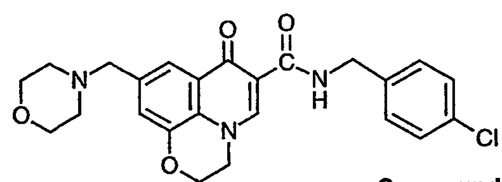

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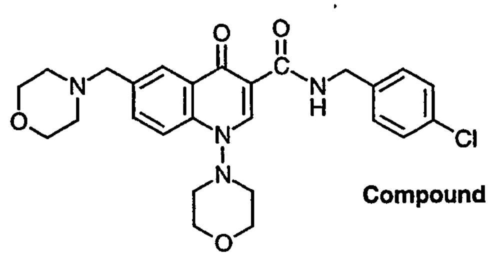
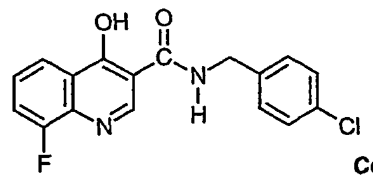
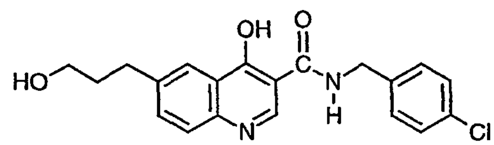


Compound No. 5

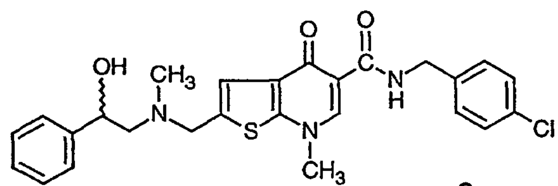
(Figure 1 continue)



Compound No. 6



Compound No. 7



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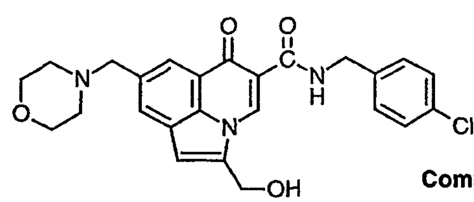
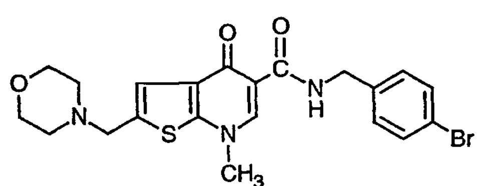
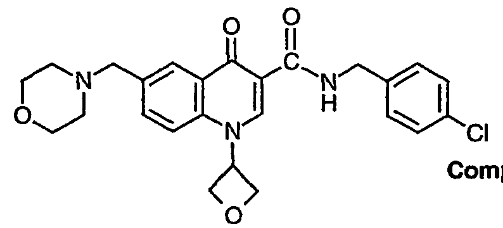


Compound No. 9

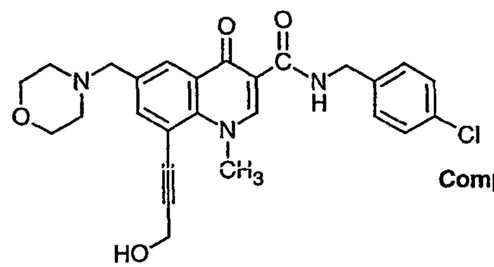


Compound No. 10

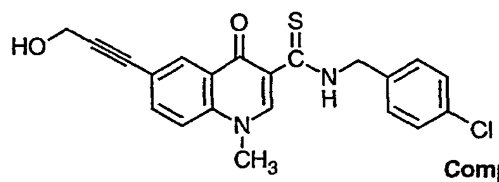
(Figure 1 continue)



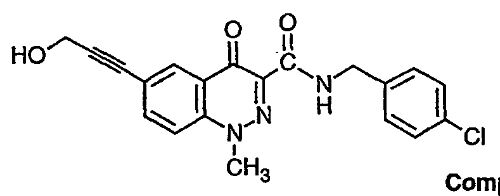
Compound No. 11



Compound No. 12

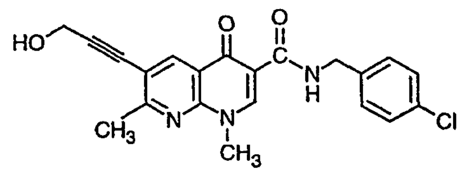


Compound No. 13

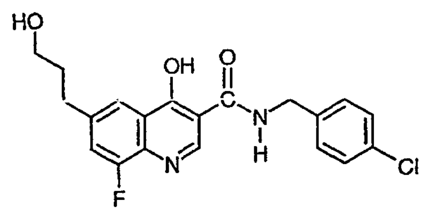


Compound No. 14

(Figure 1 continue)

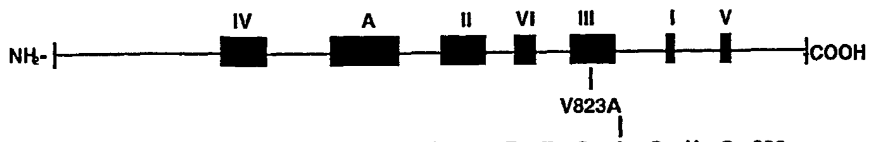


Compound No.15



Compound 17

Figure 2. The HSV1 (KOS Strain) DNA Polymerase Amino Acid 823 is Critical for Resistance to 4-Hydroxyquinolines and Related Compounds



HSV1-KOS-M1	Y	G	F	T	G	A	Q	H	G-826
HSV1	Y	G	F	T	G	V	Q	H	G-826
HSV2	Y	G	F	T	G	V	Q	H	G-829
VZV	Y	G	F	T	G	V	A	Q	G-791
EBV	Y	G	F	T	G	V	A	N	G-696
HCMV	Y	G	F	T	G	V	V	N	G-826
HHV6	Y	G	V	T	G	A	A	H	G-681
HHV7	Y	G	V	T	G	A	T	H	S-681
HHV8	Y	G	F	T	G	V	A	S	G-696

Schematic of HSV1 polymerase illustrating the conserved regions A and I-VI found in class 2 polymerases. Also shown are the amino acid sequence for the highly conserved herpesvirus domain in region III which surrounds the HSV1 amino acid 823.

Figure 3 **Serial Passage of HSV-1 in Presence of 20 µM compound 17**

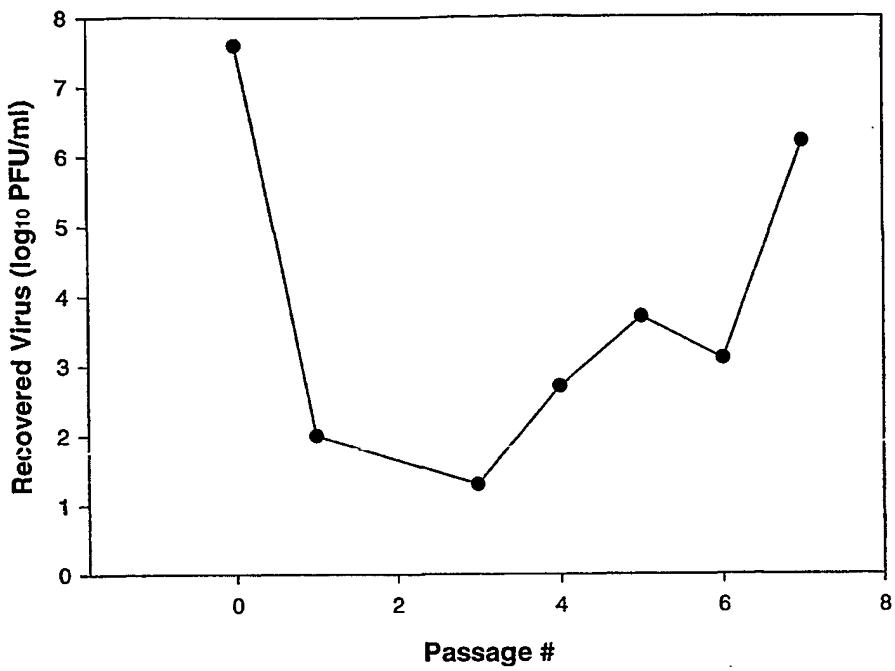


Figure 4 Comparison of Wild type HSV-1 and HSV-2 DNA Polymerases Amino Acid Sequences Alligned by Amino Acid Homology*

HSV2-MS	MFCAAGGPTS	PGGKSAARAA	SGFFAPHNPR	GATQTAPPPC	RRQNFYNPHL	-50
HSV2-186	MFCAAGGPAS	PGGKSAARAA	SGFFAPHNPR	GATQTAPPPC	RRQNFYNPHL	-50
HSV1-Kos	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
HSV1-Patton	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
HSV1-DJL	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
HSV1-F	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
HSV2-MS	AQTGTQPKAP	GPAQRHTYYS	ECDEFRFIAP	RSLDEDAPAE	QRTGVHDGRL	-100
HSV2-186	AQTGTQPKAP	GPAQRHTYYS	ECDEFRFIAP	RSLDEDAPAE	QRTGVHDGRL	-100
HSV1-Kos	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
HSV1-Patton	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
HSV1-DJl	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
HSV1-F	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
HSV2-MS	RRAPKVYCGG	DERDVLRVGP	EGFWPRRLRL	WGGADHAPKG	FDPTVTVFHV	-150
HSV2-186	RRAPKVYCGG	DERDVLRVGP	EGFWPRRLRL	WGGADHAPEG	FDPTVTVFHV	-150
HSV-Kos	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
HSV1-Patton	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
HSV1-DJL	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
HSV1-F	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
HSV2-MS	YDILEHVEHA	YSMRAAQLHE	RFMDAITPAG	TVITLLGLTP	EGHRVAVHVY	-200
HSV2-186	YDILEHVEHA	YSMRAAQLHE	RFMDAITPAG	TVITLLGLTP	EGHRVAVHVY	-200
HSV-Kos	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
HSV1-Patton	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
HSV1-DJL	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
HSV1-F	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVY	-199
HSV2-MS	GTRQYFYMNK	AEVDRHLQCR	APRDLCERLA	AALRESPGAS	FRGISADHFE	-250
HSV2-186	GTRQYFYMNK	AEVDRHLQCR	APRDLCERLA	AALRESPGAS	FRGISADHFE	-250
HSV-Kos	GTRQYFYMNK	EEVDRHLQCR	APRDLCERMA	AALRESPGAS	FRGISADHFE	-249
HSV1-Patton	GTRQYFYMNK	EEVDRHLQCR	APRDLCERMA	AALRESPGAS	FRGISADHFE	-249
HSV1-DJL	GTRQYFYMNK	EEVDRHLQCR	APRDLCERMA	AALRESPGAS	FRGISADHFE	-249
HSV1-F	GTRQYFYMNK	EEVDRHLQCR	APRDLCERMA	AALRESPGAS	FRGISADHFE	-249
HSV2-MS	AEVVERADVY	YYETRPTLYY	RVFVRSGRAL	AYLCDNFCPA	IRKYEGGVDA	-300
HSV2-186	AEVVERADVY	YYETRPTLYY	RVFVRSGRAL	AYLCDNFCPA	IRKYEGGVDA	-300
HSV-Kos	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNFCPA	IKKYEGGVDA	-299
HSV1-Patton	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNFCPA	IKKYEGGVDA	-299
HSV1-DJL	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNFCPA	IKKYEGGVDA	-299
HSV1-F	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNFCPA	IKKYEGGVDA	-299
HSV2-MS	TTRFILDNPG	FVTFGWYRLK	PGRGNAPAQP	RPPTAFGTSS	DVEFNCTADN	-350
HSV2-186	TTRFILDNPG	FVTFGWYRLK	PGRGNAPAQP	RPPTAFGTSS	DVEFNCTADN	-350
HSV-Kos	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
HSV1-Patton	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
HSV1-DJL	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
HSV1-F	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQP	RAPMAFGTSS	DVEFNCTADN	-349
HSV2-MS	LAVEGAMCDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAERPED	LVIQISCLLY	-400
HSV2-186	LAVEGAMCDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAERPED	LVIQISCLLY	-400
HSV-Kos	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
HSV1-Patton	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
HSV1-DJL	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
HSV1-F	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
HSV2-MS	DLSTTALEHI	LLFSLGSCDL	PESHLSDLAS	RGLPAPVVLE	FDSEFEMLLA	-450
HSV2-186	DLSTTALEHI	LLFSLGSCDL	PESHLSDLAS	RGLPAPVVLE	FDSEFEMLLA	-450
HSV-Kos	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449
HSV1-Patton	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449
HSV1-DJL	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449
HSV1-F	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449

HSV2-MS	FMTFVKQYGP	EFVTGYNIIN	FDWPFVLTKL	TEIYKVPLDG	YGRMNGRGVF	-500
HSV2-186	FMTFVKQYGP	EFVTGYNIIN	FDWPFVLTKL	TEIYKVPLDG	YGRMNGRGVF	-500
HSV-Kos	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
HSV1-Patton	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
HSV1-DJL	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
HSV1-F	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
HSV2-MS	RVWDIGQSHF	QKRSKIKVNG	MVNIDMYGII	TDKVKLSSYK	LNAVAEAVLK	-550
HSV2-186	RVWDIGQSHF	QKRSKIKVNG	MVNIDMYGII	TDKVKLSSYK	LNAVAEAVLK	-550
HSV-Kos	RVWDIGQSHF	QKRSKIKVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
HSV1-Patton	RVWDIGQSHF	QKRSKIKVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
HSV1-DJL	RVWDIGQSHF	QKRSKIKVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
HSV1-F	RVWDIGQSHF	QKRSKIKVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
HSV2-MS	DKKKDLSYRD	IPAYYASGPA	QRGVIGEYCV	QDSLLVGQLF	FKFLPHLELS	-600
HSV2-186	DKKKDLSYRD	IPAYYASGPA	QRGVIGEYCV	QDSLLVGQLF	FKFLPHLELS	-600
HSV-Kos	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
HSV1-Patton	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
HSV1-DJL	DKKKDLSYRD	IPTYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
HSV1-F	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
HSV2-MS	AVARLAGINI	TRTIYDGQQI	RVFTCLLRLA	GQKGFILPDT	QGRFRGLDKE	-650
HSV2-186	AVARLAGINI	TRTIYDGQQI	RVFTCLLRLA	GQKGFILPDT	QGRFRGLDKE	-650
HSV-Kos	AVARLAGINI	TRTIYDGQQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
HSV1-Patton	AVARLAGINI	TRTIYDGQQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
HSV1-DJL	AVARLAGINI	TRTIYDGQQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
HSV1-F	AVARLAGINI	TRTIYDGQQI	RVFTCLLRLA	DQKGFILPDT	QGRFRGGGGE	-649
HSV2-MS	APKRPAVPRG	EGERPGDGNG	DEDKDDDE..	DEDGDERE.E	VARETGGRHV	-697
HSV2-186	APKRPAVPRG	EGERPGDGNG	DEDKDDDEDG	DEDGDERE.E	VARETGGRHV	-697
HSV-Kos	APKRPAAARE	DEERP.....	EEEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
HSV1-Patton	APKRPAAARE	DEERP.....	EEEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
HSV1-DJL	APKRPAAARE	DEERP.....	EEEGEDENER	EEGGGEREPE	GARETAGRHV	-694
HSV1-F	APKRPAAARE	DEERP.....	EEEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
HSV2-MS	GYQGARVLDP	TSGFHVDPVV	VFDFASLYPS	IIQAHNLCFS	TLSLRPEAVA	-747
HSV2-186	GYQGARVLDP	TSGFHVDPVV	VFDFASLYPS	IIQAHNLCFS	TLSLRPEAVA	-749
HSV-Kos	GYQGARVLDP	TSGFHVNPVV	VFDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
HSV1-Patton	GYQGARVLDP	ISGFHVNPVV	VFDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
HSV1-DJL	GYQGARVLDP	TSGFHVNPVV	VFDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
HSV1-F	GYQGARVLDP	TSGFHVNPVV	VFDFASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
HSV2-MS	HLEADRDYLE	IEVGGRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-797
HSV2-186	HLEADRDYLE	IEVGGRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-799
HSV-Kos	HLEAGKDYLE	IEVGGRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
HSV1-Patton	HLEAGKDYLE	IEVGGRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
HSV1-DJL	HLEAGKDYLE	IEVGGRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
HSV1-F	HLEAGKDYLE	IEVGGRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPQ	-794
HSV2-MS	STPEEAVLLD	KQQAAIKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-847
HSV2-186	SPPEEAVLLD	KQQAAIKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-849
HSV-Kos	SSPEEAVLLD	KQQAAIKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
HSV1-Patton	SSPEEAVLLD	KQQAAIKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
HSV1-DJL	SSPEEAVLLD	KQQAAIKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
HSV1-F	SSPEEAVLLD	KQQAAIKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
HSV2-MS	LLATRAYVHA	RWAEFDQLLA	DFPEAAGMRA	PGPYSMRIIY	GDTDSIFVLC	-897
HSV2-186	LLATRAYVHA	RWAEFDQLLA	DFPEAAGMRA	PGPYSMRIIY	GDTDSIFVLC	-899
HSV-Kos	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTDSIFVLC	-894
HSV1-Patton	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTDSIFVLC	-894
HSV1-DJL	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTDSIFVLC	-894
HSV1-F	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIIY	GDTDSIFVLC	-894
HSV2-MS	RGLTAAGLVA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-947
HSV2-186	RGLTAAGLVA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-949
HSV-Kos	RGLTAAGLTA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
HSV1-Patton	RGLTAAGLTA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944

HSV1-DJL	RGLTAAGLTA	VGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
HSV1-F	RGLTAAGLTA	VGDKMASHIS	RALFLSPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
HSV2-MS	ICGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-997
HSV2-186	ICGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-999
HSV-Kos	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
HSV1-Patton	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
HSV1-DJL	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
HSV1-F	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAALAERP	-994
HSV2-MS	AEEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1047
HSV2-186	AEEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1049
HSV-Kos	AEEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
HSV1-Patton	AEEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
HSV1-DJL	AEEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
HSV1-F	AEEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
HSV2-MS	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1097
HSV2-186	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1099
HSV-Kos	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
HSV1-Patton	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
HSV1-DJL	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
HSV1-F	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
HSV2-MS	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELAE	-1147
HSV2-186	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELAE	-1149
HSV-Kos	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELAE	-1144
HSV1-Patton	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSP	ADPPGGASKP	RKLLVSELAE	-1144
HSV1-DJL	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSP	ADPPGGASKP	RKLLVSELAE	-1144
HSV1-F	ELDAAAPGDE	PAPPAALPSP	AKRPRETPLH	ADPPGGASKP	RKLLVSELAE	-1144
HSV2-MS	DPGYAIARGV	PLNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1197
HSV2-186	DPGYAIARGV	PLNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1199
HSV-Kos	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
HSV1-Patton	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
HSV1-DJL	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
HSV1-F	DPAYAIAHGV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
HSV2-MS	TWHPPDDVAA	RLRAAGFGPA	GAGATAEETR	RMLHRAFDTL	A*	-1238
HSV2-186	TWHPPDDVAA	RLRAAGFGPA	GAGATAEETR	RMLHRAFDTL	A*	-1240
HSV-Kos	VWHPPDDVAA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
HSV1-Patton	VWHPPDDVTA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
HSV1-DJL	VWHPPDDVAA	RLRTAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
HSV1-F	VWHPPDDVAA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235

*Amino acid alignment demonstrates difference in amino acid's sequences.

*The gaps "….." indicate missing amino acids relative to other stanins.

*Wild HSV2-MS is listed as SEQ. ID NO 14.

*Wild HSV2-186 is listed as SEQ. ID NO 15.

*Wild HSV-Kos is listed as SEQ. ID NO 16.

*Wild HSV1-Patton is listed as SEQ. ID NO 17.

*Wild HSV1-DJL is listed as SEQ. ID NO 18.

*Wild HSV1-F is listed as SEQ. ID NO 19.

Figure 5 **DNA and amino acid sequence list**

SEQ. ID. NO. 1 DNA sequence of DNA polymerase gene for HSV2-MS-M1

1 ATGTTTTGTG CCGCGGGCGG CCCGACTTCC CCCGGGGGGA AGTCGGCGGC
51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCCA CAACCCCCGG GGAGCCACCC
101 AGACGGCACC GCCGCCTTGC CGCCGGCAGA ACTTCTACAA CCCCCACCTC
151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC
201 GTACTACAGC GAGTGCGACG AATTTCGATT TATCGCCCCG CGTTCGCTGG
251 ACGAGGACGC CCCCGCGGAG CAGCGCACCG GGGTCCACGA CGGCCGCCTC
301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG
351 CGTGGGCCCG GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG
401 CGGACCATGC CCCCAAGGGG TTCGACCCCA CCGTCACCGT CTTCCACGTG
451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA
501 GCTCCACGAG CGATTTATGG ACGCCATCAC GCCCGCCGGG ACCGTCATCA
551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC
601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT
651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC
701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG
751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC
801 CCTGTACTAC CGCGTCTTCG TGCGAAGCGG GCGCGCGCTG GCCTACCTGT
851 GCGACAACTT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC
901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTCACCT TCGGCTGGTA
951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCCGA
1001 CGGCGTTCGG AACCTCGAGC GACGTCGAGT TTAACTGCAC GGCGGACAAC
1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG
1101 CTTCGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCCGG
1151 TCGCGGAACG CCCGGAAGAC CTCGTCATCC AGATCTCCTG TCTGCTCTAC
1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC
1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC
1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC

1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA
1401 CATCATCAAC TTCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT
1451 ACAAGGTCCC GCTCGACGGG TACGGGCGCA TGAACGGCCG GGGTGTGTTC
1501 CGCGTGTGGG ACATCGGCCA GAGCCACTTT CAGAAGCGCA GCAAGATCAA
1551 GGTGAACGGG ATGGTGAACA TCGACATGTA CGGCATCATC ACCGACAAGG
1601 TCAAACTCTC CAGCTACAAG CTGAACGCCG TCGCCGAGGC CGTCTTGAAG
1651 GACAAGAAGA AGGATCTGAG CTACCGCGAC ATCCCCGCCT ACTACGCCTC
1701 CGGGCCCGCG CAGCGCGGGG TGATCGGCGA GTATTGTGTG CAGGACTCGC
1751 TGCTGGTCGG GCAGCTGTTC TTCAAGTTTC TGCCGCACCT GGAGCTTTCC
1801 GCCGTCGCGC GCCTGGCGGG CATCAACATC ACCCGCACCA TCTACGACGG
1851 CCAGCAGATC CGCGTCTTCA CGTGCCTCCT GCGCCTTGCG GGCCAGAAGG
1901 GCTTCATCCT GCCGGACACC CAGGGGCGGT TTCGGGGCCT CGACAAGGAG
1951 GCGCCCAAGC GCCCGGCCGT GCCTCGGGGG GAAGGGGAGC GGCCGGGGGA
2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGAG GACGGGGACG
2051 AGCGCGAGGA GGTCGCGCGC GAGACCGGGG GCCGGCACGT TGGGTACCAG
2101 GGGGCCCGGG TCCTCGACCC CACCTCCGGG TTTCACGTCG ACCCCGTGGT
2151 GGTGTTTGAC TTTGCCAGCC TGTACCCCAG CATCATCCAG GCCCACAACC
2201 TGTGCTTCAG TACGCTCTCC CTGCGGCCCG AGGCCGTCGC GCACCTGGAG
2251 GCGGACCGGG ACTACCTGGA GATCGAGGTG GGGGGCCGAC GGCTGTTCTT
2301 CGTGAAGGCC CACGTACGCG AGAGCCTGCT GAGCATCCTG CTGCGCGACT
2351 GGCTGGCCAT GCGAAAGCAG ATCCGCTCGC GGATCCCCCA GAGCACCCCC
2401 GAGGAGGCCG TCCTCCTCGA CAAGCAACAG GCCGCCATCA AGGTGGTGTG
2451 CAACTCGGTG TACGGGTTCA CCGGGGCGCA GCACGGTCTT CTGCCCTGCC
2501 TGCACGTGGC CGCCACCGTG ACGACCATCG GCCGCGAGAT GCTCCTCGCG
2551 ACGCGCGCGT ACGTGCACGC GCGCTGGGCG GAGTTCGATC AGCTGCTGGC
2601 CGACTTTCCG GAGGCGGCCG GCATGCGCGC CCCCGGTCCG TACTCCATGC
2651 GCATCATCTA CGGGGACACG GACTCCATTT TCGTTTTGTG CCGCGGCCTC
2701 ACGGCCGCGG GCCTGGTGGC CATGGGCGAC AAGATGGCGA GCCACATCTC
2751 GCGCGCGCTG TTCCTCCCCC CGATCAAGCT CGAGTGCGAA AAAACGTTCA
2801 CCAAGCTGCT GCTCATCGCC AAGAAAAAGT ACATCGGCGT CATCTGCGGG

2851 GGCAAGATGC TCATCAAGGG CGTGGATCTG GTGCGCAAAA ACAACTGCGC

2901 GTTTATCAAC CGCACCTCCA GGGCCCTGGT CGACCTGCTG TTTTACGACG

2951 ATACCGTATC CGGAGCGGCC GCCGCGTTAG CCGAGCGCCC CGCAGAGGAG

3001 TGGCTGGCGC GACCCCTGCC CGAGGGACTG CAGGCGTTCG GGGCCGTCCT

3051 CGTAGACGCC CATCGGCGCA TCACCGACCC GGAGAGGGAC ATCCAGGACT

3101 TTGTCCTCAC CGCCGAACTG AGCAGACACC CGCGCGCGTA CACCAACAAG

3151 CGCCTGGCCC ACCTGACGGT GTATTACAAG CTCATGGCCC GCCGCGCGCA

3201 GGTCCCGTCC ATCAAGGACC GGATCCCGTA CGTGATCGTG GCCCAGACCC

3251 GCGAGGTAGA GGAGACGGTC GCGCGGCTGG CCGCCCTCCG CGAGCTAGAC

3301 GCCGCCGCCC CAGGGGACGA GCCCGCCCCC CCAGCGGCCC TGCCCTCCCC

3351 GGCCAAGCGC CCCCGGGAGA CGCCGTCGCA TGCCGACCCC CCGGGAGGCG

3401 CGTCCAAGCC CCGCAAGCTG CTGGTGTCCG AGCTGGCGGA GGATCCCGGG

3451 TACGCCATCG CCCGGGGCGT TCCGCTCAAC ACGGACTATT ACTTCTCGCA

3501 CCTGCTGGGG GCGGCCTGCG TGACGTTCAA GGCCCTGTTT GGAAATAACG

3551 CCAAGATCAC CGAGAGTCTG TTAAAGAGGT TTATTCCCGA GACGTGGCAC

3601 CCCCCGGACG ACGTGGCCGC GCGGCTCAGG GCCGCGGGGT TCGGGCCGGC

3651 GGGGGCCGGC GCTACGGCGG AGGAAACTCG TCGAATGTTG CATAGAGCCT

3701 TTGATACTCT AGCATGA

SEQ. ID. NO. 2 Amino acid sequence of DNA polymerase for HSV2-MS-M1

1 MFCAAGGPTS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL
51 AQTGTQPKAP GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL
101 RRAPKVYCGG DERDVLRVGP EGFWPRRLRL WGGADHAPKG FDPTVTVFHV
151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRVAVHVY
201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE
251 AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA
301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN
351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY
401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA
451 FMTFVKQYGP EFVTGYNIIN FDWPFVLTKL TEIYKVPLDG YGRMNGRGVF
501 RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK
551 DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS
601 AVARLAGINI TRTIYDGQQI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE
651 APKRPAVPRG EGERPGDGNG DEDKDDDEDE DGDEREEVAR ETGGRHVGYQ
701 GARVLDPTSG FHVDPVVVFD FASLYPSIIQ AHNLCFSTLS LRPEAVAHLE
751 ADRDYLEIEV GGRRLFFVKA HVRESLLSIL LRDWLAMRKQ IRSRIPQSTP
801 EEAVLLDKQQ AAIKVVCNSV YGFTGAQHGL LPCLHVAATV TTIGREMLLA
851 TRAYVHARWA EFDQLLADFP EAAGMRAPGP YSMRIIYGDT DSIFVLCRGL
901 TAAGLVAMGD KMASHISRAL FLPPIKLECE KTFTKLLLIA KKKYIGVICG
951 GKMLIKGVDL VRKNNCAFIN RTSRALVDLL FYDDTVSGAA AALAERPAEE
1001 WLARPLPEGL QAFGAVLVDA HRRITDPERD IQDFVLTAEL SRHPRAYTNK
1051 RLAHLTVYYK LMARRAQVPS IKDRIPYVIV AQTREVEETV ARLAALRELD
1101 AAAPGDEPAP PAALPSPAKR PRETPSHADP PGGASKPRKL LVSELAEDPG
1151 YAIARGVPLN TDYYFSHLLG AACVTFKALF GNNAKITESL LKRFIPETWH
1201 PPDDVAARLR AAGFGPAGAG ATAEETRRML HRAFDTLA*

SEQ.ID.NO. 3 DNA sequence of DNA polymerase gene for HSV2-186-M1

1 ATGTTTTGTG CCGCGGGCGG CCCGGCTTCC CCCGGGGGGA AGTCGGCGGC
51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCCA CAACCCCCGG GGAGCCACCC
101 AGACGGCACC GCCGCCTTGC CGCCGGCAGA ACTTCTACAA CCCCCACCTC
151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC
201 GTACTACAGC GAGTGCGACG AATTTCGATT TATCGCCCCG CGTTCGCTGG
251 ACGAGGACGC CCCCGCGGAG CAGCGCACCG GGGTCCACGA CGGCCGCCTC
301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG
351 CGTGGGCCCG GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG
401 CGGACCATGC CCCCGAGGGG TTCGACCCCA CCGTCACCGT CTTCCACGTG
451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA
501 GCTCCACGAG CGATTTATGG ACGCCATCAC GCCCGCCGGG ACCGTCATCA
551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC
601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT
651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC
701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG
751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC
801 CCTGTACTAC CGCGTCTTCG TGCGAAGCGG GCGCGCGCTG GCCTACCTGT
851 GCGACAACTT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC
901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTCACCT TCGGCTGGTA
951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCCGA
1001 CGGCGTTCGG AACCTCGAGC GACGTCGAGT TTAACTGCAC GGCGGACAAC
1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG
1101 CTTCGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCCGG
1151 TCGCGGAACG CCCGGAAGAC CTCGTCATCC AGATCTCCTG TCTGCTCTAC
1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC
1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC
1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC
1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA
1401 CATCATCAAC TTCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT

1451 ACAAGGTCCC GCTCGACGGG TACGGGCGCA TGAACGGCCG GGGTGTGTTC
1501 CGCGTGTGGG ACATCGGCCA GAGCCACTTT CAGAAGCGCA GCAAGATCAA
1551 GGTGAACGGG ATGGTGAACA TCGACATGTA CGGCATCATC ACCGACAAGG
1601 TCAAACTCTC CAGCTACAAG CTGAACGCCG TCGCCGAGGC CGTCTTGAAG
1651 GACAAGAAGA AGGATCTGAG CTACCGCGAC ATCCCCGCCT ACTACGCCTC
1701 CGGGCCCGCG CAGCGCGGGG TGATCGGCGA GTATTGTGTG CAGGACTCGC
1751 TGCTGGTCGG GCAGCTGTTC TTCAAGTTTC TGCCGCACCT GGAGCTTTCC
1801 GCCGTCGCGC GCCTGGCGGG CATCAACATC ACCCGCACCA TCTACGACGG
1851 CCAGCAGATC CGCGTCTTCA CGTGCCTCCT GCGCCTTGCG GGCCAGAAGG
1901 GCTTCATCCT GCCGGACACC CAGGGGCGGT TTCGGGGCCT CGACAAGGAG
1951 GCGCCCAAGC GCCCGGCCGT GCCTCGGGGG GAAGGGGAGC GGCCGGGGGA
2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGGG GACGAGGACG
2051 GGGACGAGCG CGAGGAGGTC GCGCGCGAGA CCGGGGGCCG GCACGTTGGG
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2151 CGTGGTGGTG TTTGACTTTG CCAGCCTGTA CCCCAGCATC ATCCAGGCCC
2201 ACAACCTGTG CTTCAGTACG CTCTCCCTGC GGCCCGAGGC CGTCGCGCAC
2251 CTGGAGGCGG ACCGGGACTA CCTGGAGATC GAGGTGGGGG GCCGACGGCT
2301 GTTCTTCGTG AAGGCCCACG TACGCGAGAG CCTGCTGAGC ATCCTGCTGC
2351 GCGACTGGCT GGCCATGCGA AAGCAGATCC GCTCGCGGAT CCCCCAGAGC
2401 CCCCCCGAGG AGGCCGTCCT CCTCGACAAG CAACAGGCCG CCATCAAGGT
2451 GGTGTGCAAC TCGGTGTACG GGTTCACCGG GGCGCAGCAC GGTCTTCTGC
2501 CCTGCCTGCA CGTGGCCGCC ACCGTGACGA CCATCGGCCG CGAGATGCTC
2551 CTCGCGACGC GCGCGTACGT GCACGCGCGC TGGGCGGAGT TCGATCAGCT
2601 GCTGGCCGAC TTTCCGGAGG CGGCCGGCAT GCGCGCCCCC GGTCCGTACT
2651 CCATGCGCAT CATCTACGGG GACACGGACT CCATTTTCGT TTTGTGCCGC
2701 GGCCTCACGG CCGCGGGCCT GGTGGCCATG GGCGACAAGA TGGCGAGCCA
2751 CATCTCGCGC GCGCTGTTCC TCCCCCCGAT CAAGCTCGAG TGCGAAAAAA
2801 CGTTCACCAA GCTGCTGCTC ATCGCCAAGA AAAAGTACAT CGGCGTCATC
2851 TGCGGGGGCA AGATGCTCAT CAAGGGCGTG GATCTGGTGC GCAAAAACAA
2901 CTGCGCGTTT ATCAACCGCA CCTCCAGGGC CCTGGTCGAC CTGCTGTTTT

2951 ACGACGATAC CGTATCCGGA GCGGCCGCCG CGTTAGCCGA GCGCCCCGCA

3001 GAGGAGTGGC TGGCGCGACC CCTGCCCGAG GGACTGCAGG CGTTCGGGGC

3051 CGTCCTCGTA GACGCCCATC GGCGCATCAC CGACCCGGAG AGGGACATCC

3101 AGGACTTTGT CCTCACCGCC GAACTGAGCA GACACCCGCG CGCGTACACC

3151 AACAAGCGCC TGGCCCACCT GACGGTGTAT TACAAGCTCA TGGCCCGCCG

3201 CGCGCAGGTC CCGTCCATCA AGGACCGGAT CCCGTACGTG ATCGTGGCCC

3251 AGACCCGCGA GGTAGAGGAG ACGGTCGCGC GGCTGGCCGC CCTCCGCGAG

3301 CTAGACGCCG CCGCCCCAGG GGACGAGCCC GCCCCCCCAG CGGCCCTGCC

3351 CTCCCCGGCC AAGCGCCCCC GGGAGACGCC GTCGCATGCC GACCCCCCGG

3401 GAGGCGCGTC CAAGCCCCGC AAGCTGCTGG TGTCCGAGCT GGCGGAGGAT

3451 CCCGGGTACG CCATCGCCCG GGGCGTTCCG CTCAACACGG ACTATTACTT

3501 CTCGCACCTG CTGGGGGCGG CCTGCGTGAC GTTCAAGGCC CTGTTTGGAA

3551 ATAACGCCAA GATCACCGAG AGTCTGTTAA AGAGGTTTAT TCCCGAGACG

3601 TGGCACCCCC CGGACGACGT GGCCGCGCGG CTCAGGGCCG CGGGGTTCGG

3651 GCCGGCGGGG GCCGGCGCTA CGGCGGAGGA AACTCGTCGA ATGTTGCATA

3701 GAGCCTTTGA TACTCTAGCA TGA

SEQ.ID.NO. 4 Amino acid sequence of DNA polymerase for HSV2-186-M1

1 MFCAAGGPAS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL

51 AQTGTQPKAP GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL

101 RRAPKVYCGG DERDVLRVGP EGFWPRRLRL WGGADHAPEG FDPTVTVFHV

151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRVAVHVY

201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE

251 AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA

301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN

351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY

401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA

451 FMTFVKQYGP EFVTGYNIIN FDWPFVLTKL TEIYKVPLDG YGRMNGRGVF

501 RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK

551 DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS

601 AVARLAGINI TRTIYDGQQI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE

651 APKRPAVPRG EGERPGDGNG DEDKDDDEDG DEDGDEREEV ARETGGRHVG

701 YQGARVLDPT SGFHVDPVVV FDFASLYPSI IQAHNLCFST LSLRPEAVAH

751 LEADRDYLEI EVGGRRLFFV KAHVRESLLS ILLRDWLAMR KQIRSRIPQS

801 PPEEAVLLDK QQAAIKVVCN SVYGFTGAQH GLLPCLHVAA TVTTIGREML

851 LATRAYVHAR WAEFDQLLAD FPEAAGMRAP GPYSMRIIYG DTDSIFVLCR

901 GLTAAGLVAM GDKMASHISR ALFLPPIKLE CEKTFTKLLL IAKKKYIGVI

951 CGGKMLIKGV DLVRKNNCAF INRTSRALVD LLFYDDTVSG AAAALAERPA

1001 EEWLARPLPE GLQAFGAVLV DAHRRITDPE RDIQDFVLTA ELSRHPRAYT

1051 NKRLAHLTVY YKLMARRAQV PSIKDRIPYV IVAQTREVEE TVARLAALRE

1101 LDAAAPGDEP APPAALPSPA KRPRETPSHA DPPGGASKPR KLLVSELAED

1151 PGYAIARGVP LNTDYYFSHL LGAACVTFKA LFGNNAKITE SLLKRFIPET

1201 WHPPDDVAAR LRAAGFGPAG AGATAEETRR MLHRAFDTLA *

SEQ.ID.NO. 5 DNA sequence of DNA polymerase gene for HSV1-KOS-M1

1 ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
101 GGGGACCCCC GCCTTGTTTG AGGCAAAACT TTTACAACCC CTACCTCGCC
151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
201 CTATAGCGAA TGCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
401 ACCACGCCCC GGCGGGGTTC AACCCCACCG TCACCGTCTT TCACGTGTAC
451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAGTT
501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA
651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
701 AGTCCCCGGG CGCGTCGTTC CGCGGCATCT CCGCGGACCA CTTCGAGGCG
751 GAGGTGGTGG AGCGCACCGA CGTGTACTAC TACGAGACGC GCCCCGCTCT
801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCG TACCTGTGCG
851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
901 ACCCGGTTCA TCCTGGACAA CCCCGGGTTC GTCACCTTCG GCTGGTACCG
951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
1001 CCTTCGGGAC ATCCAGCGAC GTCGAGTTTA ACTGTACGGC GGACAACCTG
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1151 CCGGGCACCC GGAGGACCTG GTTATTCAGA TATCCTGTCT GCTCTACGAC
1201 CTGTCCACCA CCGCCCTGGA GCACGTCCTC CTGTTTTCGC TCGGTTCCTG
1251 CGACCTCCCC GAATCCCACC TGAACGAGCT GGCGGCCAGG GGCCTGCCCA
1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
1351 ATGACCCTTG TGAAACAGTA CGGCCCCGAG TTCGTGACCG GGTACAACAT
1401 CATCAACTTC GACTGGCCCT TCTTGCTGGC CAAGTTGACG GACATTTACA

1451 AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
1501 GTGTGGGACA TAGGCCAGAG CCACTTCCAG AAGCGCAGCA AGATAAAGGT
1551 GAACGGCATG GTGAACATCG ACATGTACGG GATCATAACC GACAAGATCA
1601 AGCTCTCGAG CTACAAGCTC AACGCCGTGG CCGAAGCCGT CCTGAAGGAC
1651 AAGAAGAAGG ACCTGAGCTA TCGCGACATC CCCGCCTACT ACGCCGCCGG
1701 GCCCGCGCAA CGCGGGGTGA TCGGCGAGTA CTGCATACAG GATTCCCTGC
1751 TGGTGGGCCA GCTGTTTTTT AAGTTTTTGC CCCATCTGGA GCTCTCGGCC
1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA
1851 GCAGATCCGC GTCTTTACGT GCCTGCTGCG CCTGGCCGAC CAGAAGGGCT
1901 TTATTCTGCC GGACACCCAG GGGCGATTTA GGGGCGCCGG GGGGGAGGCG
1951 CCCAAGCGTC CGGCCGCAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA
2001 GGGGGAGGAC GAGGACGAAC GCGAGGAGGG CGGGGGCGAG CGGGAGCCGG
2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG
2101 GTCCTTGACC CCACTTCCGG GTTTCACGTG AACCCCGTGG TGGTGTTCGA
2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCCACAAC CTGTGCTTCA
2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG
2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC
2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA
2351 TGCGAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC
2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACTCGGT
2451 GTACGGGTTC ACGGGAGCGC AGCACGGACT CCTGCCGTGC CTGCACGTTG
2501 CCGCGACGGT GACGACCATC GGCCGCGAGA TGCTGCTCGC GACCCGCGAG
2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCC
2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT
2651 ACGGGGACAC GGACTCCATA TTTGTGCTGT GCCGCGGCCT CACGGCCGCC
2701 GGGCTGACGG CCATGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT
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2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG
2851 CTCATCAAGG GCGTGGATCT GGTGCGCAAA AACAACTGCG CGTTTATCAA
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2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG
3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC
3051 CCATCGGCGC ATCACCGACC CGGAGAGGGA CATCCAGGAC TTTGTCCTCA
3101 CCGCCGAACT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC
3151 CACCTGACGG TGTATTACAA GCTCATGGCC CGCCGCGCGC AGGTCCCGTC
3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCCAGACC CGCGAGGTAG
3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTAGA CGCCGCCGCC
3301 CCAGGGGACG AGCCCGCCCC CCCCGCGGCC CTGCCCTCCC CGGCCAAGCG
3351 CCCCCGGGAG ACGCCGTCGC ATGCCGACCC CCCGGGAGGC GCGTCCAAGC
3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT
3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG
3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGGAC
3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG
3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
3701 TAGCATGA

SEQ.ID.NO. 6 Amino acid sequence of DNA polymerase for HSV1-KOS-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA

51 PVGTQQKPTG PTQRHTYYSE CDEFRFIAPR VLDEDAPPEK RAGVHDGHLK

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151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVYG

201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA

251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT

301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL

351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD

401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF

451 MTLVKQYGPE FVTGYNIINF DWPFLLAKLT DIYKVPLDGY GRMNGRGVFR

501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD

551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA

601 VARLAGINIT RTIYDGQQIR VFTCLLRLAD QKGFILPDTQ GRFRGAGGEA

651 PKRPAAARED EERPEEEGED EDEREEGGGE REPEGARETA GRHVGYQGAR

701 VLDPTSGFHV NPVVVFDFAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK

751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA

801 VLLDKQQAAI KVVCNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE

851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIIYGDTDSI FVLCRGLTAA

901 GLTAMGDKMA SHISRALFLP PIKLECEKTF TKLLLIAKKK YIGVIYGGKM

951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAEEWLA

1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA

1051 HLTVYYKLMA RRAQVPSIKD RIPYVIVAQT REVEETVARL AALRELDAAA

1101 PGDEPAPPAA LPSPAKRPRE TPSHADPPGG ASKPRKLLVS ELAEDPAYAI

1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD

1201 DVAARLRAAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 7 DNA sequence of HSV polymerase gene for HSV1-F-M1

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  51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
 101 GGGGACCCCC GCCTTGCTTG AGGCAAAACT TTTACAACCC CTACCTCGCC
 151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
 201 CTATAGCGAA TGCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
 251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
 301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
 351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
 401 ACCACGCCCC GGCGGGGTTC AACCCCACCG TCACCGTCTT TCACGTGTAC
 451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAGTT
 501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
 551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
 601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTCGACA GGCACCTACA
 651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
 701 AGTCCCCGGG CGCGTCGTTC CGCGGCATTT CCGCGGACCA CTTCGAGGCG
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1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
1351 ATGACCCTTG TGAAACAGTA CGGCCCCGAG TTCGTGACCG GGTACAACAT
1401 CATCAACTTC GACTGGCCCT TCTTGCTGGC CAAGCTGACG GACATTTACA
1451 AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
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1551 GAACGGCATG GTGAACATCG ACATGTACGG GATTATAACC GACAAGATCA
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2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG
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2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCC
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3151 CACCTGACGG TGTATTACAA GCTCATGGCC CGCCGCGCGC AGGTCCCGTC
3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCCAGACC CGCGAGGTAG

3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTCGA CGCCGCCGCC
3301 CCAGGGGACG AGCCCGCCCC CCCCGCGGCC CTGCCCTCCC CGGCCAAGCG
3351 CCCCCGGGAG ACGCCGTTGC ATGCCGACCC CCCGGGAGGC GCGTCCAAGC
3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT
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3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGGAC
3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG
3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
3701 TAGCATGA

SEQ.ID.NO. 8 Amino acid sequence of DNA polymerase for HSV1-F-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA

51 PVGTQQKPTG PTQRHTYYSE CDEFRFIAPR VLDEDAPPEK RAGVHDGHLK

101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY

151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVYG

201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA

251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT

301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL

351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD

401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF

451 MTLVKQYGPE FVTGYNIINF DWPFLLAKLT DIYKVPLDGY GRMNGRGVFR

501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD

551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA

601 VARLAGINIT RTIYDGQQIR VFTCLLRLAD QKGFILPDTQ GRFRGGGGEA

651 PKRPAAARED EERPEEEGED EDEREEGGGE REPEGARETA GRHVGYQGAR

701 VLDPTSGFHV NPVVVFDFAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK

751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA

801 VLLDKQQAAI KVVCNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE

851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIIYGDTDSI FVLCRGLTAA

901 GLTAVGDKMA SHISRALFLS PIKLECEKTF TKLLLIAKKK YIGVIYGGKM

951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAEEWLA

1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA

1051 HLTVYYKLMA RRAQVPSIKD RIPYVIVAQT REVEETVARL AALRELDAAA

1101 PGDEPAPPAA LPSPAKRPRE TPLHADPPGG ASKPRKLLVS ELAEDPAYAI

1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD

1201 DVAARLRAAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 9 DNA sequence of HSV polymerase gene for HSV1-DJL-M1

1 ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
101 GGGGACCCCC GCCTTGTTTG AGGCAAAACT TTTACAACCC CTACCTCGCC
151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
201 CTATAGCGAA TGCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
401 ACCACGCCCC GGCGGGGTTC AACCCCACCG TCACCGTCTT TCACGTGTAT
451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCCAGTT
501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA
651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
701 AGTCCCCGGG CGCGTCGTTC CGCGGCATCT CCGCGGACCA CTTCGAGGCG
751 GAGGTGGTGG AGCGCACCGA CGTGTACTAC TACGAGACGC GCCCCGCTCT
801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCG TACCTGTGCG
851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
901 ACCCGGTTCA TCCTGGACAA CCCCGGGTTC GTCACCTTCG GCTGGTACCG
951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
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3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGGAC
3601 GACGTGGCCG CGCGGCTCCG GACCGCAGGG TTCGGGGCGG TGGGTGCCGG
3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
3701 TAGCATGA

SEQ.ID.NO. 10 Amino acid sequence of DNA polymerase for HSV1-DJL-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA

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101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY

151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVYG

201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA

251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT

301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL

351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD

401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF

451 MTLVKQYGPE FVTGYNIINF DWPFLLAKLT DIYKVPLDGY GRMNGRGVFR

501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD

551 KKKDLSYRDI PTYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA

601 VARLAGINIT RTIYDGQQIR VFTCLLRLAD QKGFILPDTQ GRFRGAGGEA

651 PKRPAAARED EERPEEEGED ENEREEGGGE REPEGARETA GRHVGYQGAR

701 VLDPTSGFHV NPVVVFDFAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK

751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA

801 VLLDKQQAAI KVVCNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE

851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIIYGDTDSI FVLCRGLTAA

901 GLTAVGDKMA SHISRALFLP PIKLECEKTF TKLLLIAKKK YIGVIYGGKM

951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAEEWLA

1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA

1051 HLTVYYKLMA RRAQVPSIKD RIPYVIVAQT REVEETVARL AALRELDAAA

1101 PGDEPAPPAA LPSPAKRPRE TPSPADPPGG ASKPRKLLVS ELAEDPAYAI

1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD

1201 DVAARLRTAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 11 DNA sequence of DNA polymerase gene for HMCV-AD169-M1

1 ATGTTTTTCA ACCCGTATCT GAGCGGCGGC GTGACCGGCG GTGCGGTCGC
51 GGGTGGCCGG CGTCAGCGTT CGCAGCCCGG CTCCGCGCAG GGCTCGGGCA
101 AGCGGCCGCC ACAGAAACAG TTTTTGCAGA TCGTGCCGCG AGGTGTCATG
151 TTCGACGGTC AGACGGGGTT GATCAAGCAT AAGACGGGAC GGCTGCCTCT
201 CATGTTCTAT CGAGAGATTA AACATTTGTT GAGTCATGAC ATGGTTTGGC
251 CGTGTCCTTG GCGCGAGACC CTGGTGGGTC GCGTGGTGGG ACCTATTCGT
301 TTTCACACCT ACGATCAGAC GGACGCCGTG CTCTTCTTCG ACTCGCCCGA
351 AAACGTGTCG CCGCGCTATC GTCAGCATCT GGTGCCTTCG GGGAACGTGT
401 TGCGTTTCTT CGGGGCCACA GAACACGGCT ACAGTATCTG CGTCAACGTT
451 TTCGGGCAGC GCAGCTACTT TTACTGTGAG TACAGCGACA CCGATAGGCT
501 GCGTGAGGTC ATTGCCAGCG TGGGCGAACT AGTGCCCGAA CCGCGGACGC
551 CATACGCCGT GTCTGTCACG CCGGCCACCA AGACCTCCAT CTATGGGTAC
601 GGGACGCGAC CCGTGCCCGA TTTGCAGTGT GTGTCTATCA GCAACTGGAC
651 CATGGCCAGA AAAATCGGCG AGTATCTGCT GGAGCAGGGT TTTCCCGTGT
701 ACGAGGTCCG TGTGGATCCG CTGACGCGTT TGGTCATCGA TCGGCGGATC
751 ACCACGTTCG GCTGGTGCTC CGTGAATCGT TACGACTGGC GGCAGCAGGG
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901 GATATCGAGT GCATGAGCGG CGAGGGTGGT TTTCCCTGCG CCGAGAAGTC
951 CGATGACATT GTCATTCAGA TCTCGTGCGT GTGCTACGAG ACGGGGGGAA
1001 ACACCGCCGT GGATCAGGGG ATCCCAAACG GGAACGATGG TCGGGGCTGC
1051 ACTTCGGAGG GTGTGATCTT TGGGCACTCG GGTCTTCATC TCTTTACGAT
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SEQ.ID.NO.12 **Amino acid sequence of DNA polymerase for HCMV-AD169-M1**

1 MFFNPYLSGG VTGGAVAGGR RQRSQPGSAQ GSGKRPPQKQ FLQIVPRGVM
51 FDGQTGLIKH KTGRLPLMFY REIKHLLSHD MVWPCPWRET LVGRVVGPIR
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251 TTFGWCSVNR YDWRQQGRAS TCDIEVDCDV SDLVAVPDDS SWPRYRCLSF
301 DIECMSGEGG FPCAEKSDDI VIQISCVCYE TGGNTAVDQG IPNGNDGRGC
351 TSEGVIFGHS GLHLFTIGTC GQVGPDVDVY EFPSEYELLL GFMLFFQRYA
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Figure 6

SEQ.ID.NO.13 Amino acid sequence of DNA polymerase for HCMV-AD169

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SEQUENCE LISTING

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<120> A Method for Treating Herpes Virus

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His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
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Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
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Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
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Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
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Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu
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Arg Leu Trp Gly Gly Ala Asp His Ala Pro Glu Gly Phe Asp Pro Thr
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Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala

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Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
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His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
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Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
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Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
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Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
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Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
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Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
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Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
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Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
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Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
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Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
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Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
        355                 360                 365

Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
    370                 375                 380

Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
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Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
                405                 410                 415

Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
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Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
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Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
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Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
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Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
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Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
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Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
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Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
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Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
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Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
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Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
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Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
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Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
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Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu
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Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala
690 695 700

Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val
705 710 715 720

Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu
725 730 735

Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu
740 745 750

Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe
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Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg
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Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser
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Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
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Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu
820 825 830

Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
835 840 845

Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
850 855 860

Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
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Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
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Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
900 905 910

Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
915 920 925

Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
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Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
945 950 955 960

Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
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Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
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Ala Ala Leu Ala Glu Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu
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Pro Glu Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His
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Arg Arg Ile Thr Asp Pro Glu Arg Asp Ile Gln Asp Phe Val Leu
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Thr Ala Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg
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Gln Val Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala
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Ala Ala Leu Pro Ser Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser
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His Ala Asp Pro Pro Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu

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Val Ser Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly
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Val Pro Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala
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Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
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His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
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Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
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Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
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Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
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Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val

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Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
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Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
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Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
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245 250 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
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Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
275 280 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
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Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
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Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
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Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
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Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
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Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385 390 395 400

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Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
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Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
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Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
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Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
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Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
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Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
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Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
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Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
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Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
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Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
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Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
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Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
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Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
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Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
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Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
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Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
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Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
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Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
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Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800
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Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
915 920 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
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Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
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Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
965 970 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
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Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
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Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
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Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
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Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
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Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
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Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
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Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
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Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
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Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser His Ala Asp Pro Pro

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Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
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Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
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Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
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Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
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Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
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Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
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35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
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His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg

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Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
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Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
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Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
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Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
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Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
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Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
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Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
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Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
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Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
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Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
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Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
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Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
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Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
485 490 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
500 505 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
515 520 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
530 535 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545 550 555 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
565 570 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
580 585 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
595 600 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
610 615 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625 630 635 640

Gly Arg Phe Arg Gly Gly Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
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Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
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Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
675 680 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
690 695 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705 710 715 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
725 730 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
740 745 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
755 760 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
770 775 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785 790 795 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
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Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
820 825 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
850 855 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865 870 875 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
885 890 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
900 905 910

Ile Ser Arg Ala Leu Phe Leu Ser Pro Ile Lys Leu Glu Cys Glu Lys
915 920 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
930 935 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
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Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
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Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
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Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
995 1000 1005

Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
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Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
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Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
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Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
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Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
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Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
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Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser

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Pro Ala Lys Arg Pro Arg Glu Thr Pro Leu His Ala Asp Pro Pro
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Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
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Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
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Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
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Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
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Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
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Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
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Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
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Leu Ala
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Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg

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Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
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Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
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Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430
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Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Thr Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asn
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765
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Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
770 775 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785 790 795 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
805 810 815

Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
820 825 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
850 855 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865 870 875 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
885 890 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
900 905 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
915 920 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
930 935 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945 950 955 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
965 970 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
980 985 990

Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
995 1000 1005

Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
1010 1015 1020

Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
1025 1030 1035

Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
1040 1045 1050

Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
1055 1060 1065

Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
1070 1075 1080

Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala

1085 1090 1095

Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
1100 1105 1110

Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro
1115 1120 1125

Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
1130 1135 1140

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
1145 1150 1155

Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
1175 1180 1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
1190 1195 1200

Ala Arg Leu Arg Thr Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
1205 1210 1215

Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
1220 1225 1230

Leu Ala
1235

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tttttgcaga tcgtgccgcg aggtgtcatg ttcgacggtc agacggggtt gatcaagcat 180

aagacgggac ggctgcctct catgttctat cgagagatta aacatttgtt gagtcatgac 240

atggtttggc cgtgtccttg gcgcgagacc ctggtgggtc gcgtggtggg acctattcgt 300

tttcacacct acgatcagac ggacgccgtg ctcttcttcg actcgcccga aaacgtgtcg 360

ccgcgctatc gtcagcatct ggtgccttcg gggaacgtgt tgcgtttctt cggggccaca 420

gaacacggct acagtatctg cgtcaacgtt ttcgggcagc gcagctactt ttactgtgag 480

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gggacgcgac ccgtgcccga tttgcagtgt gtgtctatca gcaactggac catggccaga 660

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gatatcgagt gcatgagcgg cgagggtggt tttccctgcg ccgagaagtc cgatgacatt 960

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atcccgcgtt gtttcgtggc taatgccgag ggccgcgccc aggtaggccg ttactgtctg 1620

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cgtatctaca cctcgctgct ggacgagtgc gcctgccgcg attttatcct gcccaaccac 1800

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gtgtttgagc ccgaggtggg ttactacaac gaccccgtgg ccgtgttcga ctttgccagc 2160

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cgggtggagg cgcgggtcat ctacggggac acggacagcg tgtttgtccg ctttcgtggc 2760

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ggcgtgccca ttcacgccga caagtacttt gagcaggttc tcaaggctgt aactaacgtg 3600

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tgctgttga 3729

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<213> herpes simplex

<400> 12

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Ala Gly Gly Arg Arg Gln Arg Ser Gln Pro Gly Ser Ala Gln Gly Ser
20 25 30

Gly Lys Arg Pro Pro Gln Lys Gln Phe Leu Gln Ile Val Pro Arg Gly
35 40 45

Val Met Phe Asp Gly Gln Thr Gly Leu Ile Lys His Lys Thr Gly Arg
50 55 60

Leu Pro Leu Met Phe Tyr Arg Glu Ile Lys His Leu Leu Ser His Asp
65 70 75 80

Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
                85   90   95

Gly Pro Ile Arg Phe His Thr Tyr Asp Gln Thr Asp Ala Val Leu Phe
            100   105   110

Phe Asp Ser Pro Glu Asn Val Ser Pro Arg Tyr Arg Gln His Leu Val
        115   120   125

Pro Ser Gly Asn Val Leu Arg Phe Phe Gly Ala Thr Glu His Gly Tyr
    130   135   140

Ser Ile Cys Val Asn Val Phe Gly Gln Arg Ser Tyr Phe Tyr Cys Glu
145   150   155   160

Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
                165   170   175

Leu Val Pro Glu Pro Arg Thr Pro Tyr Ala Val Ser Val Thr Pro Ala
            180   185   190

Thr Lys Thr Ser Ile Tyr Gly Tyr Gly Thr Arg Pro Val Pro Asp Leu
        195   200   205

Gln Cys Val Ser Ile Ser Asn Trp Thr Met Ala Arg Lys Ile Gly Glu
    210   215   220

Tyr Leu Leu Glu Gln Gly Phe Pro Val Tyr Glu Val Arg Val Asp Pro
225   230   235   240

Leu Thr Arg Leu Val Ile Asp Arg Arg Ile Thr Thr Phe Gly Trp Cys
                245   250   255

Ser Val Asn Arg Tyr Asp Trp Arg Gln Gln Gly Arg Ala Ser Thr Cys
            260   265   270

Asp Ile Glu Val Asp Cys Asp Val Ser Asp Leu Val Ala Val Pro Asp
        275   280   285

Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
    290   295   300

Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
305   310   315   320

Val Ile Gln Ile Ser Cys Val Cys Tyr Glu Thr Gly Gly Asn Thr Ala
                325   330   335

Val Asp Gln Gly Ile Pro Asn Gly Asn Asp Gly Arg Gly Cys Thr Ser
            340   345   350

Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
        355   360   365

Thr Cys Gly Gln Val Gly Pro Asp Val Asp Val Tyr Glu Phe Pro Ser
    370   375   380

Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
385   390   395   400

Pro Ala Phe Val Thr Gly Tyr Asn Ile Asn Ser Phe Asp Leu Lys Tyr

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                405                 410                 415

Ile Leu Thr Arg Leu Glu Tyr Leu Tyr Lys Val Asp Ser Gln Arg Phe
            420                 425                 430

Cys Lys Leu Pro Thr Ala Gln Gly Gly Arg Phe Phe Leu His Ser Pro
        435                 440                 445

Ala Val Gly Phe Lys Arg Gln Tyr Ala Ala Ala Phe Pro Ser Ala Ser
    450                 455                 460

His Asn Asn Pro Ala Ser Thr Ala Ala Thr Lys Val Tyr Ile Ala Gly
465                 470                 475                 480

Ser Val Val Ile Asp Met Tyr Pro Val Cys Met Ala Lys Thr Asn Ser
                485                 490                 495

Pro Asn Tyr Lys Leu Asn Thr Met Ala Glu Leu Tyr Leu Arg Gln Arg
            500                 505                 510

Lys Asp Asp Leu Ser Tyr Lys Asp Ile Pro Arg Cys Phe Val Ala Asn
        515                 520                 525

Ala Glu Gly Arg Ala Gln Val Gly Arg Tyr Cys Leu Gln Asp Ala Val
    530                 535                 540

Leu Val Arg Asp Leu Phe Asn Thr Ile Asn Phe His Tyr Glu Ala Gly
545                 550                 555                 560

Ala Ile Ala Arg Leu Ala Lys Ile Pro Leu Arg Arg Val Ile Phe Asp
                565                 570                 575

Gly Gln Gln Ile Arg Ile Tyr Thr Ser Leu Leu Asp Glu Cys Ala Cys
            580                 585                 590

Arg Asp Phe Ile Leu Pro Asn His Tyr Ser Lys Gly Thr Thr Val Pro
        595                 600                 605

Glu Thr Asn Ser Val Ala Val Ser Pro Asn Ala Ala Ile Ile Ser Thr
    610                 615                 620

Ala Ala Val Pro Gly Asp Ala Gly Ser Val Ala Ala Met Phe Gln Met
625                 630                 635                 640

Ser Pro Pro Leu Gln Ser Ala Pro Ser Ser Gln Asp Gly Val Ser Pro
                645                 650                 655

Gly Ser Gly Ser Asn Ser Ser Ser Ser Val Gly Val Phe Ser Val Gly
            660                 665                 670

Ser Gly Ser Ser Gly Gly Val Gly Val Ser Asn Asp Asn His Gly Ala
        675                 680                 685

Gly Gly Thr Ala Ala Val Ser Tyr Gln Gly Ala Thr Val Phe Glu Pro
    690                 695                 700

Glu Val Gly Tyr Tyr Asn Asp Pro Val Ala Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Met Ala His Asn Leu Cys Tyr Ser Thr Leu
                725                 730                 735
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Leu Val Pro Gly Gly Glu Tyr Pro Val Asp Pro Ala Asp Val Tyr Ser
740 745 750

Val Thr Leu Glu Asn Gly Val Thr His Arg Phe Val Arg Ala Ser Val
755 760 765

Arg Val Ser Val Leu Ser Glu Leu Leu Asn Lys Trp Val Ser Gln Arg
770 775 780

Arg Ala Val Arg Glu Cys Met Arg Glu Cys Gln Asp Pro Val Arg Arg
785 790 795 800

Met Leu Leu Asp Lys Glu Gln Met Ala Leu Lys Val Thr Cys Asn Ala
805 810 815

Phe Tyr Gly Phe Thr Gly Ala Leu Asn Gly Met Met Pro Cys Leu Pro
820 825 830

Ile Ala Ala Ser Ile Thr Arg Ile Gly Arg Asp Met Leu Glu Arg Thr
835 840 845

Ala Arg Phe Ile Lys Asp Asn Phe Ser Glu Pro Cys Phe Leu His Asn
850 855 860

Phe Phe Asn Gln Glu Asp Tyr Val Val Gly Thr Arg Glu Gly Asp Ser
865 870 875 880

Glu Glu Ser Ser Ala Leu Pro Glu Gly Leu Glu Thr Ser Ser Gly Gly
885 890 895

Ser Asn Glu Arg Arg Val Glu Ala Arg Val Ile Tyr Gly Asp Thr Asp
900 905 910

Ser Val Phe Val Arg Phe Arg Gly Leu Thr Pro Gln Ala Leu Val Ala
915 920 925

Arg Gly Pro Ser Leu Ala His Tyr Val Thr Ala Cys Leu Phe Val Glu
930 935 940

Pro Val Lys Leu Glu Phe Glu Lys Val Phe Val Ser Leu Met Met Ile
945 950 955 960

Cys Lys Lys Arg Tyr Ile Gly Lys Val Glu Gly Ala Ser Gly Leu Ser
965 970 975

Met Lys Gly Val Asp Leu Val Arg Lys Thr Ala Cys Glu Phe Val Lys
980 985 990

Gly Val Thr Arg Asp Val Leu Ser Leu Leu Phe Glu Asp Arg Glu Val
995 1000 1005

Ser Glu Ala Ala Val Arg Leu Ser Arg Leu Ser Leu Asp Glu Val
1010 1015 1020

Lys Lys Tyr Gly Val Pro Arg Gly Phe Trp Arg Ile Leu Arg Arg
1025 1030 1035

Leu Val Gln Ala Arg Asp Asp Leu Tyr Leu His Arg Val Arg Val
1040 1045 1050

Glu Asp Leu Val Leu Ser Ser Val Leu Ser Lys Asp Ile Ser Leu
1055 1060 1065

Tyr Arg Gln Ser Asn Leu Pro His Ile Ala Val Ile Lys Arg Leu
1070 1075 1080

Ala Ala Arg Ser Glu Glu Leu Pro Ser Val Gly Asp Arg Val Phe
1085 1090 1095

Tyr Val Leu Thr Ala Pro Gly Val Arg Thr Ala Pro Gln Gly Ser
1100 1105 1110

Ser Asp Asn Gly Asp Ser Val Thr Ala Gly Val Val Ser Arg Ser
1115 1120 1125

Asp Ala Ile Asp Gly Thr Asp Asp Asp Ala Asp Gly Gly Gly Val
1130 1135 1140

Glu Glu Ser Asn Arg Arg Gly Gly Glu Pro Ala Lys Lys Arg Ala
1145 1150 1155

Arg Lys Pro Pro Ser Ala Val Cys Asn Tyr Glu Val Ala Glu Asp
1160 1165 1170

Pro Ser Tyr Val Arg Glu His Gly Val Pro Ile His Ala Asp Lys
1175 1180 1185

Tyr Phe Glu Gln Val Leu Lys Ala Val Thr Asn Val Leu Ser Pro
1190 1195 1200

Val Phe Pro Gly Gly Glu Thr Ala Arg Lys Asp Lys Phe Leu His
1205 1210 1215

Met Val Leu Pro Arg Arg Leu His Leu Glu Pro Ala Phe Leu Pro
1220 1225 1230

Tyr Ser Val Lys Ala His Glu Cys Cys
1235 1240

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<400> 13

Met Phe Phe Asn Pro Tyr Leu Ser Gly Gly Val Thr Gly Gly Ala Val
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Ala Gly Gly Arg Arg Gln Arg Ser Gln Pro Gly Ser Ala Gln Gly Ser
20 25 30

Gly Lys Arg Pro Pro Gln Lys Gln Phe Leu Gln Ile Val Pro Arg Gly
35 40 45

Val Met Phe Asp Gly Gln Thr Gly Leu Ile Lys His Lys Thr Gly Arg
50 55 60

Leu Pro Leu Met Phe Tyr Arg Glu Ile Lys His Leu Leu Ser His Asp
65 70 75 80

Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
85 90 95

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Gly Pro Ile Arg Phe His Thr Tyr Asp Gln Thr Asp Ala Val Leu Phe
            100                 105                 110

Phe Asp Ser Pro Glu Asn Val Ser Pro Arg Tyr Arg Gln His Leu Val
        115                 120                 125

Pro Ser Gly Asn Val Leu Arg Phe Phe Gly Ala Thr Glu His Gly Tyr
    130                 135                 140

Ser Ile Cys Val Asn Val Phe Gly Gln Arg Ser Tyr Phe Tyr Cys Glu
145                 150                 155                 160

Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
                165                 170                 175

Leu Val Pro Glu Pro Arg Thr Pro Tyr Ala Val Ser Val Thr Pro Ala
            180                 185                 190

Thr Lys Thr Ser Ile Tyr Gly Tyr Gly Thr Arg Pro Val Pro Asp Leu
        195                 200                 205

Gln Cys Val Ser Ile Ser Asn Trp Thr Met Ala Arg Lys Ile Gly Glu
    210                 215                 220

Tyr Leu Leu Glu Gln Gly Phe Pro Val Tyr Glu Val Arg Val Asp Pro
225                 230                 235                 240

Leu Thr Arg Leu Val Ile Asp Arg Arg Ile Thr Thr Phe Gly Trp Cys
                245                 250                 255

Ser Val Asn Arg Tyr Asp Trp Arg Gln Gln Gly Arg Ala Ser Thr Cys
            260                 265                 270

Asp Ile Glu Val Asp Cys Asp Val Ser Asp Leu Val Ala Val Pro Asp
        275                 280                 285

Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
    290                 295                 300

Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
305                 310                 315                 320

Val Ile Gln Ile Ser Cys Val Cys Tyr Glu Thr Gly Gly Asn Thr Ala
                325                 330                 335

Val Asp Gln Gly Ile Pro Asn Gly Asn Asp Gly Arg Gly Cys Thr Ser
            340                 345                 350

Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
        355                 360                 365

Thr Cys Gly Gln Val Gly Pro Asp Val Asp Val Tyr Glu Phe Pro Ser
    370                 375                 380

Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
385                 390                 395                 400

Pro Ala Phe Val Thr Gly Tyr Asn Ile Asn Ser Phe Asp Leu Lys Tyr
                405                 410                 415

Ile Leu Thr Arg Leu Glu Tyr Leu Tyr Lys Val Asp Ser Gln Arg Phe
            420                 425                 430
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Cys Lys Leu Pro Thr Ala Gln Gly Gly Arg Phe Phe Leu His Ser Pro
        435   440   445

Ala Val Gly Phe Lys Arg Gln Tyr Ala Ala Ala Phe Pro Ser Ala Ser
    450   455   460

His Asn Asn Pro Ala Ser Thr Ala Ala Thr Lys Val Tyr Ile Ala Gly
465   470   475   480

Ser Val Val Ile Asp Met Tyr Pro Val Cys Met Ala Lys Thr Asn Ser
                485   490   495

Pro Asn Tyr Lys Leu Asn Thr Met Ala Glu Leu Tyr Leu Arg Gln Arg
            500   505   510

Lys Asp Asp Leu Ser Tyr Lys Asp Ile Pro Arg Cys Phe Val Ala Asn
        515   520   525

Ala Glu Gly Arg Ala Gln Val Gly Arg Tyr Cys Leu Gln Asp Ala Val
    530   535   540

Leu Val Arg Asp Leu Phe Asn Thr Ile Asn Phe His Tyr Glu Ala Gly
545   550   555   560

Ala Ile Ala Arg Leu Ala Lys Ile Pro Leu Arg Arg Val Ile Phe Asp
                565   570   575

Gly Gln Gln Ile Arg Ile Tyr Thr Ser Leu Leu Asp Glu Cys Ala Cys
            580   585   590

Arg Asp Phe Ile Leu Pro Asn His Tyr Ser Lys Gly Thr Thr Val Pro
        595   600   605

Glu Thr Asn Ser Val Ala Val Ser Pro Asn Ala Ala Ile Ile Ser Thr
    610   615   620

Ala Ala Val Pro Gly Asp Ala Gly Ser Val Ala Ala Met Phe Gln Met
625   630   635   640

Ser Pro Pro Leu Gln Ser Ala Pro Ser Ser Gln Asp Gly Val Ser Pro
                645   650   655

Gly Ser Gly Ser Asn Ser Ser Ser Ser Val Gly Val Phe Ser Val Gly
            660   665   670

Ser Gly Ser Ser Gly Gly Val Gly Val Ser Asn Asp Asn His Gly Ala
        675   680   685

Gly Gly Thr Ala Ala Val Ser Tyr Gln Gly Ala Thr Val Phe Glu Pro
    690   695   700

Glu Val Gly Tyr Tyr Asn Asp Pro Val Ala Val Phe Asp Phe Ala Ser
705   710   715   720

Leu Tyr Pro Ser Ile Ile Met Ala His Asn Leu Cys Tyr Ser Thr Leu
                725   730   735

Leu Val Pro Gly Gly Glu Tyr Pro Val Asp Pro Ala Asp Val Tyr Ser
            740   745   750

Val Thr Leu Glu Asn Gly Val Thr His Arg Phe Val Arg Ala Ser Val

755 760 765

Arg Val Ser Val Leu Ser Glu Leu Leu Asn Lys Trp Val Ser Gln Arg
770 775 780

Arg Ala Val Arg Glu Cys Met Arg Glu Cys Gln Asp Pro Val Arg Arg
785 790 795 800

Met Leu Leu Asp Lys Glu Gln Met Ala Leu Lys Val Thr Cys Asn Ala
805 810 815

Phe Tyr Gly Phe Thr Gly Val Val Asn Gly Met Met Pro Cys Leu Pro
820 825 830

Ile Ala Ala Ser Ile Thr Arg Ile Gly Arg Asp Met Leu Glu Arg Thr
835 840 845

Ala Arg Phe Ile Lys Asp Asn Phe Ser Glu Pro Cys Phe Leu His Asn
850 855 860

Phe Phe Asn Gln Glu Asp Tyr Val Val Gly Thr Arg Glu Gly Asp Ser
865 870 875 880

Glu Glu Ser Ser Ala Leu Pro Glu Gly Leu Glu Thr Ser Ser Gly Gly
885 890 895

Ser Asn Glu Arg Arg Val Glu Ala Arg Val Ile Tyr Gly Asp Thr Asp
900 905 910

Ser Val Phe Val Arg Phe Arg Gly Leu Thr Pro Gln Ala Leu Val Ala
915 920 925

Arg Gly Pro Ser Leu Ala His Tyr Val Thr Ala Cys Leu Phe Val Glu
930 935 940

Pro Val Lys Leu Glu Phe Glu Lys Val Phe Val Ser Leu Met Met Ile
945 950 955 960

Cys Lys Lys Arg Tyr Ile Gly Lys Val Glu Gly Ala Ser Gly Leu Ser
965 970 975

Met Lys Gly Val Asp Leu Val Arg Lys Thr Ala Cys Glu Phe Val Lys
980 985 990

Gly Val Thr Arg Asp Val Leu Ser Leu Leu Phe Glu Asp Arg Glu Val
995 1000 1005

Ser Glu Ala Ala Val Arg Leu Ser Arg Leu Ser Leu Asp Glu Val
1010 1015 1020

Lys Lys Tyr Gly Val Pro Arg Gly Phe Trp Arg Ile Leu Arg Arg
1025 1030 1035

Leu Val Gln Ala Arg Asp Asp Leu Tyr Leu His Arg Val Arg Val
1040 1045 1050

Glu Asp Leu Val Leu Ser Ser Val Leu Ser Lys Asp Ile Ser Leu
1055 1060 1065

Tyr Arg Gln Ser Asn Leu Pro His Ile Ala Val Ile Lys Arg Leu
1070 1075 1080

Ala Ala Arg Ser Glu Glu Leu Pro Ser Val Gly Asp Arg Val Phe
1085 1090 1095

Tyr Val Leu Thr Ala Pro Gly Val Arg Thr Ala Pro Gln Gly Ser
1100 1105 1110

Ser Asp Asn Gly Asp Ser Val Thr Ala Gly Val Val Ser Arg Ser
1115 1120 1125

Asp Ala Ile Asp Gly Thr Asp Asp Asp Ala Asp Gly Gly Gly Val
1130 1135 1140

Glu Glu Ser Asn Arg Arg Gly Gly Glu Pro Ala Lys Lys Arg Ala
1145 1150 1155

Arg Lys Pro Pro Ser Ala Val Cys Asn Tyr Glu Val Ala Glu Asp
1160 1165 1170

Pro Ser Tyr Val Arg Glu His Gly Val Pro Ile His Ala Asp Lys
1175 1180 1185

Tyr Phe Glu Gln Val Leu Lys Ala Val Thr Asn Val Leu Ser Pro
1190 1195 1200

Val Phe Pro Gly Gly Glu Thr Ala Arg Lys Asp Lys Phe Leu His
1205 1210 1215

Met Val Leu Pro Arg Arg Leu His Leu Glu Pro Ala Phe Leu Pro
1220 1225 1230

Tyr Ser Val Lys Ala His Glu Cys Cys
1235 1240

<210> 14
<211> 1238
<212> PRT
<213> herpes simplex

<400> 14

Met Phe Cys Ala Ala Gly Gly Pro Thr Ser Pro Gly Gly Lys Ser Ala
1 5 10 15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro His Asn Pro Arg Gly Ala
20 25 30

Thr Gln Thr Ala Pro Pro Pro Cys Arg Arg Gln Asn Phe Tyr Asn Pro
35 40 45

His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
50 55 60

Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
65 70 75 80

Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
85 90 95

Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
100 105 110

Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu

115 120 125

Arg Leu Trp Gly Gly Ala Asp His Ala Pro Lys Gly Phe Asp Pro Thr
130 135 140

Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala
145 150 155 160

Tyr Ser Met Arg Ala Ala Gln Leu His Glu Arg Phe Met Asp Ala Ile
165 170 175

Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
180 185 190

His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
195 200 205

Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
210 215 220

Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
225 230 235 240

Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
245 250 255

Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
260 265 270

Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
275 280 285

Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
290 295 300

Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
305 310 315 320

Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
325 330 335

Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
340 345 350

Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
355 360 365

Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
370 375 380

Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
385 390 395 400

Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
405 410 415

Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
420 425 430

Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
435 440 445

Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
    450   455   460

Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
465   470   475   480

Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
                485   490   495

Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
            500   505   510

Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
        515   520   525

Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
    530   535   540

Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
545   550   555   560

Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
                565   570   575

Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
            580   585   590

Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
        595   600   605

Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
    610   615   620

Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
625   630   635   640

Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
                645   650   655

Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
            660   665   670

Asp Lys Asp Asp Asp Glu Asp Glu Asp Gly Asp Glu Arg Glu Glu Val
        675   680   685

Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val
    690   695   700

Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val Phe Asp
705   710   715   720

Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe
                725   730   735

Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu Ala Asp
            740   745   750

Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val
        755   760   765

Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp
    770   775   780

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Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Thr Pro
785                 790                 795                 800

Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val
                805                 810                 815

Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro
            820                 825                 830

Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu
        835                 840                 845

Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe Asp Gln
    850                 855                 860

Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro Gly Pro
865                 870                 875                 880

Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu
                885                 890                 895

Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp Lys Met
            900                 905                 910

Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu
        915                 920                 925

Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr
    930                 935                 940

Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu
945                 950                 955                 960

Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu
                965                 970                 975

Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala
            980                 985                 990

Leu Ala Glu Arg Pro Ala Glu Glu  Trp Leu Ala Arg Pro  Leu Pro Glu
        995                 1000                 1005

Gly Leu  Gln Ala Phe Gly Ala  Val Leu Val Asp Ala  His Arg Arg
    1010                 1015                 1020

Ile Thr  Asp Pro Glu Arg Asp  Ile Gln Asp Phe Val  Leu Thr Ala
    1025                 1030                 1035

Glu Leu  Ser Arg His Pro Arg  Ala Tyr Thr Asn Lys  Arg Leu Ala
    1040                 1045                 1050

His Leu  Thr Val Tyr Tyr Lys  Leu Met Ala Arg Arg  Ala Gln Val
    1055                 1060                 1065

Pro Ser  Ile Lys Asp Arg Ile  Pro Tyr Val Ile Val  Ala Gln Thr
    1070                 1075                 1080

Arg Glu  Val Glu Glu Thr Val  Ala Arg Leu Ala Ala  Leu Arg Glu
    1085                 1090                 1095

Leu Asp  Ala Ala Ala Pro Gly  Asp Glu Pro Ala Pro  Pro Ala Ala
```

1100 1105 1110

Leu Pro Ser Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser His Ala
1115 1120 1125

Asp Pro Pro Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser
1130 1135 1140

Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly Val Pro
1145 1150 1155

Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys
1160 1165 1170

Val Thr Phe Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu
1175 1180 1185

Ser Leu Leu Lys Arg Phe Ile Pro Glu Thr Trp His Pro Pro Asp
1190 1195 1200

Asp Val Ala Ala Arg Leu Arg Ala Ala Gly Phe Gly Pro Ala Gly
1205 1210 1215

Ala Gly Ala Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala
1220 1225 1230

Phe Asp Thr Leu Ala
1235

<210> 15
<211> 1240
<212> PRT
<213> herpes simplex

<400> 15

Met Phe Cys Ala Ala Gly Gly Pro Ala Ser Pro Gly Gly Lys Ser Ala
1 5 10 15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro His Asn Pro Arg Gly Ala
20 25 30

Thr Gln Thr Ala Pro Pro Pro Cys Arg Arg Gln Asn Phe Tyr Asn Pro
35 40 45

His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
50 55 60

Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
65 70 75 80

Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
85 90 95

Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
100 105 110

Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu
115 120 125

Arg Leu Trp Gly Gly Ala Asp His Ala Pro Glu Gly Phe Asp Pro Thr
130 135 140

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Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala
145                 150                 155                 160

Tyr Ser Met Arg Ala Ala Gln Leu His Glu Arg Phe Met Asp Ala Ile
                165                 170                 175

Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
            180                 185                 190

His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
        195                 200                 205

Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
    210                 215                 220

Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
225                 230                 235                 240

Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
                245                 250                 255

Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
            260                 265                 270

Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
        275                 280                 285

Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
    290                 295                 300

Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
305                 310                 315                 320

Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
                325                 330                 335

Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
            340                 345                 350

Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
        355                 360                 365

Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
    370                 375                 380

Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
385                 390                 395                 400

Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
                405                 410                 415

Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
            420                 425                 430

Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
        435                 440                 445

Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
    450                 455                 460

Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
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465 470 475 480

Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
485 490 495

Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
500 505 510

Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
515 520 525

Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
530 535 540

Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
545 550 555 560

Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
565 570 575

Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
580 585 590

Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
595 600 605

Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
610 615 620

Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
625 630 635 640

Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
645 650 655

Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
660 665 670

Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu
675 680 685

Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala
690 695 700

Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val
705 710 715 720

Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu
725 730 735

Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu
740 745 750

Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe
755 760 765

Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg
770 775 780

Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser
785 790 795 800

Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
805 810 815

Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu
820 825 830

Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
835 840 845

Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
850 855 860

Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
865 870 875 880

Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
885 890 895

Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
900 905 910

Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
915 920 925

Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
930 935 940

Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
945 950 955 960

Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
965 970 975

Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
980 985 990

Ala Ala Leu Ala Glu Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu
995 1000 1005

Pro Glu Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His
1010 1015 1020

Arg Arg Ile Thr Asp Pro Glu Arg Asp Ile Gln Asp Phe Val Leu
1025 1030 1035

Thr Ala Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg
1040 1045 1050

Leu Ala His Leu Thr Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala
1055 1060 1065

Gln Val Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala
1070 1075 1080

Gln Thr Arg Glu Val Glu Glu Thr Val Ala Arg Leu Ala Ala Leu
1085 1090 1095

Arg Glu Leu Asp Ala Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro
1100 1105 1110

Ala Ala Leu Pro Ser Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser
1115 1120 1125

His Ala Asp Pro Pro Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu
1130 1135 1140

Val Ser Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly
1145 1150 1155

Val Pro Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala
1160 1165 1170

Ala Cys Val Thr Phe Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile
1175 1180 1185

Thr Glu Ser Leu Leu Lys Arg Phe Ile Pro Glu Thr Trp His Pro
1190 1195 1200

Pro Asp Asp Val Ala Ala Arg Leu Arg Ala Ala Gly Phe Gly Pro
1205 1210 1215

Ala Gly Ala Gly Ala Thr Ala Glu Glu Thr Arg Arg Met Leu His
1220 1225 1230

Arg Ala Phe Asp Thr Leu Ala
1235 1240

<210> 16
<211> 1235
<212> PRT
<213> herpes simplex

<400> 16

Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1 5 10 15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
20 25 30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
115 120 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
130 135 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145 150 155 160

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Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495
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```
Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
                565                 570                 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
            580                 585                 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
        595                 600                 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
    610                 615                 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625                 630                 635                 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
                645                 650                 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
            660                 665                 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
        675                 680                 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
    690                 695                 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705                 710                 715                 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
                725                 730                 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
            740                 745                 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
        755                 760                 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
    770                 775                 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785                 790                 795                 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
                805                 810                 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
```

820 825 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
850 855 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865 870 875 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
885 890 895

Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
900 905 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
915 920 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
930 935 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945 950 955 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
965 970 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
980 985 990

Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
995 1000 1005

Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
1010 1015 1020

Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
1025 1030 1035

Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
1040 1045 1050

Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
1055 1060 1065

Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
1070 1075 1080

Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
1085 1090 1095

Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
1100 1105 1110

Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser His Ala Asp Pro Pro
1115 1120 1125

Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
1130 1135 1140

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
1145 1150 1155

Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
1175 1180 1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
1190 1195 1200

Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
1205 1210 1215

Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
1220 1225 1230

Leu Ala
1235

<210> 17
<211> 1235
<212> PRT
<213> herpes simplex

<400> 17

Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1 5 10 15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
20 25 30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
115 120 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
130 135 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145 150 155 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
165 170 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His

```
        180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510
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Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
515 520 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
530 535 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545 550 555 560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
565 570 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
580 585 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
595 600 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
610 615 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625 630 635 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
645 650 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
660 665 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
675 680 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
690 695 700

Ile Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705 710 715 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
725 730 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
740 745 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
755 760 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
770 775 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785 790 795 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
805 810 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
820 825 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
850 855 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865 870 875 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
885 890 895

Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
900 905 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
915 920 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
930 935 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945 950 955 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
965 970 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
980 985 990

Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
995 1000 1005

Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
1010 1015 1020

Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
1025 1030 1035

Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
1040 1045 1050

Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
1055 1060 1065

Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
1070 1075 1080

Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
1085 1090 1095

Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
1100 1105 1110

Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro
1115 1120 1125

Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
1130 1135 1140

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
1145 1150 1155

Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe

1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
1175 1180 1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Thr
1190 1195 1200

Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
1205 1210 1215

Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
1220 1225 1230

Leu Ala
1235

<210> 18
<211> 1235
<212> PRT
<213> herpes simplex

<400> 18

Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1 5 10 15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
20 25 30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
115 120 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
130 135 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145 150 155 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
165 170 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
180 185 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
195 200 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
210 215 220

Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225 230 235 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
245 250 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
260 265 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
275 280 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
290 295 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305 310 315 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
325 330 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
340 345 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
355 360 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
370 375 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385 390 395 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
405 410 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
420 425 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
435 440 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
450 455 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465 470 475 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
485 490 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
500 505 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
515 520 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala

530 535 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545 550 555 560

Pro Thr Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
565 570 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
580 585 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
595 600 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
610 615 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625 630 635 640

Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
645 650 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asn
660 665 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
675 680 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
690 695 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705 710 715 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
725 730 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
740 745 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
755 760 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
770 775 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785 790 795 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
805 810 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
820 825 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
850 855 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865 870 875 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
885 890 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
900 905 910

Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
915 920 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
930 935 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945 950 955 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
965 970 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
980 985 990

Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
995 1000 1005

Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
1010 1015 1020

Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
1025 1030 1035

Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
1040 1045 1050

Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
1055 1060 1065

Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
1070 1075 1080

Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
1085 1090 1095

Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
1100 1105 1110

Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro
1115 1120 1125

Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
1130 1135 1140

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
1145 1150 1155

Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
1175 1180 1185

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Lys Arg  Phe Ile Pro Glu Val  Trp His Pro Pro Asp  Asp Val Ala
    1190                 1195                 1200

Ala Arg  Leu Arg Thr Ala Gly  Phe Gly Ala Val Gly  Ala Gly Ala
    1205                 1210                 1215

Thr Ala  Glu Glu Thr Arg Arg  Met Leu His Arg Ala  Phe Asp Thr
    1220                 1225                 1230

Leu Ala
    1235

<210>  19
<211>  1235
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<213>  herpes simplex

<400>  19

Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
1               5                   10                  15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
            20                  25                  30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
        35                  40                  45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
    50                  55                  60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65                  70                  75                  80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
                85                  90                  95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
            100                 105                 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
        115                 120                 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
    130                 135                 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
145                 150                 155                 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
                165                 170                 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
            180                 185                 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
        195                 200                 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
    210                 215                 220
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Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
225                 230                 235                 240

Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
                245                 250                 255

Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
            260                 265                 270

Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
        275                 280                 285

Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
    290                 295                 300

Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
305                 310                 315                 320

Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
                325                 330                 335

Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
            340                 345                 350

Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
        355                 360                 365

Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
    370                 375                 380

Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
385                 390                 395                 400

Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
                405                 410                 415

Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
            420                 425                 430

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
        435                 440                 445

Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
    450                 455                 460

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
465                 470                 475                 480

Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
                485                 490                 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
            500                 505                 510

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
        515                 520                 525

Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
    530                 535                 540

Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
545                 550                 555                 560
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Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
565 570 575

Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
580 585 590

Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
595 600 605

Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
610 615 620

Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
625 630 635 640

Gly Arg Phe Arg Gly Gly Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
645 650 655

Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
660 665 670

Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
675 680 685

Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
690 695 700

Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
705 710 715 720

Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
725 730 735

Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
740 745 750

Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
755 760 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
770 775 780

Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
785 790 795 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
805 810 815

Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
820 825 830

Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
850 855 860

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
865 870 875 880

Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly

885 890 895

Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
900 905 910

Ile Ser Arg Ala Leu Phe Leu Ser Pro Ile Lys Leu Glu Cys Glu Lys
915 920 925

Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
930 935 940

Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
945 950 955 960

Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
965 970 975

Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
980 985 990

Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
995 1000 1005

Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
1010 1015 1020

Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
1025 1030 1035

Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
1040 1045 1050

Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
1055 1060 1065

Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
1070 1075 1080

Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
1085 1090 1095

Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
1100 1105 1110

Pro Ala Lys Arg Pro Arg Glu Thr Pro Leu His Ala Asp Pro Pro
1115 1120 1125

Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
1130 1135 1140

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
1145 1150 1155

Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
1160 1165 1170

Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
1175 1180 1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
1190 1195 1200

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Ala Arg  Leu Arg Ala Ala Gly  Phe Gly Ala Val Gly  Ala Gly Ala
    1205                 1210                 1215

Thr Ala  Glu Glu Thr Arg Arg  Met Leu His Arg Ala  Phe Asp Thr
    1220                 1225                 1230

Leu Ala
    1235
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